OPEN ACCESS
OPUS AUGSBURG

Universität Augsburg
Universitätsbibliothek

Does size matter? Center-specific characteristics and survival after allogeneic hematopoietic cell transplantation for acute myeloid leukemia: an analysis of the German Registry for Stem Cell Transplantation and Cell Therapy

Wolfgang Bethge, Sarah Flossdorf, Franziska Hanke, Christoph Schmid, Mark Ringhoffer, Stefan Klein, Bernd Hertenstein, Johannes Schetelig, Matthias Stelljes, Thomas Schroeder, Igor Wolfgang Blau, Francis Ayuk, Matthias Eder, Robert Zeiser, Katharina Fleischhauer, Nicolaus Kröger, Peter Dreger

Angaben zur Veröffentlichung / Publication details:

Bethge, Wolfgang, Sarah Flossdorf, Franziska Hanke, Christoph Schmid, Mark Ringhoffer, Stefan Klein, Bernd Hertenstein, et al. 2025. "Does size matter? Center-specific characteristics and survival after allogeneic hematopoietic cell transplantation for acute myeloid leukemia: an analysis of the German Registry for Stem Cell Transplantation and Cell Therapy." *Haematologica* 110 (6): 1292–1303. https://doi.org/10.3324/haematol.2024.286385.

Nutzungsbedingungen / Terms of use: **CC BY-NC 4.0**

Dieses Dokument wird unter folgenden Bedingungen zur Verfügung gestellt: / This document is made available under these conditions:
CC-BY-NC 4.0: Creative Commons: Namensnennung - Nicht kommerziell
Weitere Informationen finden Sie unter: / For more information see:
https://creativecommons.org/licenses/by-nc/4.0/deed.de

Does size matter? Center-specific characteristics and survival after allogeneic hematopoietic cell transplantation for acute myeloid leukemia: an analysis of the German Registry for Stem Cell Transplantation and Cell Therapy

Wolfgang Bethge,[1,2] Sarah Flossdorf,[3,4] Franziska Hanke,[4] Christoph Schmid,[5] Mark Ringhoffer,[6] Stefan Klein,[7] Bernd Hertenstein,[8] Johannes Schetelig,[2,9] Matthias Stelljes,[2,10] Thomas Schroeder,[11] Igor Wolfgang Blau,[12] Francis Ayuk,[2,13] Matthias Eder,[14] Robert Zeiser,[15] Katharina Fleischhauer,[4,11] Nicolaus Kröger[4,13] and Peter Dreger;[2,16] on behalf of the German Working Group for Hematopoietic Stem Cell Transplantation and Cellular Therapy e.V. (DAG-HSZT) and the German Registry for Hematopoietic Stem Cell Transplantation and Cell Therapy (DRST)

[1]University Hospital Tübingen, Tübingen; [2]German Working Group for Hematopoietic Stem Cell Transplantation and Cellular Therapy; [3]Institute for Medical Informatics, Biometry, and Epidemiology, University Hospital Essen, University of Duisburg-Essen, Essen; [4]German Registry for Hematopoietic Stem Cell Transplantation and Cell Therapy, Ulm; [5]University Hospital Augsburg, Augsburg; [6]Hospital Karlsruhe, Karlsruhe; [7]University Hospital Mannheim, Mannheim; [8]Central Hospital Bremen, Bremen; [9]University Hospital Dresden, Dresden; [10]University Hospital Muenster, Muenster; [11]University Hospital Essen, Essen; [12]University Hospital Charité Berlin, Berlin; [13]University Medical Center Hamburg, Hamburg; [14]University Hospital Hannover, Hannover; [15]University Hospital Freiburg, Freiburg and [16]University Hospital Heidelberg, Heidelberg, Germany

Correspondence: W. Bethge
wolfgang.bethge@med.uni-tuebingen.de

Received: August 5, 2024.
Accepted: November 28, 2024.
Early view: December 5, 2024.

https://doi.org/10.3324/haematol.2024.286385

©2025 Ferrata Storti Foundation
Published under a CC BY-NC license

Abstract

We investigated the effect of center-specific variables on overall survival (OS) after allogeneic hematopoietic cell transplantation (alloHCT) in acute myeloid leukemia (AML). Eligible for the study were adult patients reported to the German Registry for Hematopoietic Stem Cell Transplantation and Cell Therapy (DRST) receiving first alloHCT for AML from a related or matched (>9/10 HLA-match) unrelated donor in the period 2015-2021. Primary endpoint was OS at 12 months from alloHCT. Univariable and multivariable analyses after best subset selection were performed. Of 5,328 patients, 83% received alloHCT in a high-volume center (≥40 alloHCT/year), 90% in a university hospital, 90% in a center performing alloHCT for ≥10 years, and 73% in a Joint Accreditation Committee ISCT-Europe & European Group for Blood and Marrow Transplantation (EBMT) (JACIE) accredited center. 52% of the patients were in first CR, and European LeukemiaNet risk was adverse in 37% and intermediate in 42%. On multivariable analysis, center-specific factors predicting adverse 12-month OS were program duration <5-10 years (Hazard Ratio [HR] 1.23, [95% Confidence Interval: [1.02; 1.49]), center volume <40 alloHCT/year (HR 1.21, [1.02; 1.45]), and treatment at a non-university hospital (HR 1.21, [0.98; 1.49]), whereas JACIE accreditation did not. Spline modeling suggested a negative effect of a center volume up to 45 alloHCT per year. Center volume, center experience, university hospital, but not JACIE accreditation, have an impact on alloHCT outcomes in adult patients with AML in Germany.

Introduction

While patient-, disease- and procedure-related outcome predictors in allogeneic hematopoietic cell transplantation (alloHCT) for acute myeloid leukemia (AML) are well characterized, the impact of center-specific variables on outcomes are still a matter of debate. Standards of patient selection, conditioning regimen selection, graft-*versus*-host

disease (GvHD) prophylaxis and supportive care practice, as well as outpatient follow-up programs and infrastructure may vary considerably between centers and health care systems.[1-4] Furthermore, center size, experience, and staff expertise, in addition to the frequency of alloHCT performed, may influence the quality of patient care and alloHCT outcome.[5-7]

Recently, German health authorities redefined the volume of alloHCT per center in Germany required to qualify for reimbursement at ≥40 alloHCT per year. This decision was largely based on a recent CIBMTR analysis by Majhail *et al.* reporting this threshold as outcome-relevant for alloHCT in the US.[8] As health systems, infrastructure, and treatment practices may widely differ between countries, the purpose of the present study was for the first time to investigate the effects of center-related factors, such as numbers of alloHCT procedures per year, program duration, university hospital, and Joint Accreditation Committee ISCT-Europe & European Group for Blood and Marrow Transplantation (EBMT) accreditation (JACIE), adjusted for common disease- and transplant-specific confounders on survival after alloHCT in Germany, using AML as a standard indication. To address these questions, we took advantage of the German Registry for Hematopoietic Stem Cell Transplantation and Cell Therapy (DRST), the German national partner of the EBMT.

Methods

Data source

The DRST is a registered association that maintains the German Registry for Hematopoietic Stem Cell Transplantation and Cell Therapy. The DRST performs data collection of hematopoietic cell transplantations (HCT) and cellular therapies in Germany in cooperation with the EBMT using the EBMT database. Accreditation as a DRST center requires a signed tripartite Joint Controllership Agreement with the EBMT and the DRST, and the submission of core data from all consecutive HCT and cellular therapy recipients to the EBMT Registry in which patients can be identified by the diagnosis of underlying disease and the type of HCT or cellular therapy. As part of the JACIE certification, EBMT/DRST registry data are routinely audited to determine accuracy of data collected. Data collection requires written informed consent using a consent form based on a standard DRST/EBMT template following the European data protection regulations and the principles of the Declaration of Helsinki.

Study design

This study was performed at the request of the DAG-HSZT (German Working Group for Hematopoietic Stem Cell Transplantation and Cellular Therapy) and was approved by the data access commission of the DRST.

The study was performed in accordance with the Declaration of Helsinki and approved by the Ethical Committee of the University of Tuebingen (Ref. Nr. 277/2020BO2).

Adult (≥18 years) patients with AML with any disease status treated with a first allogeneic HCT using a peripheral blood or bone marrow graft from a matched or mismatched related (including haploidentical) or (9/10-10/10 HLA-compatible) unrelated donor between 2015 and 2021 and registered with the DRST were eligible for the study.

The objective of the study was to assess the impact on outcome of allogeneic HCT of center-specific factors such as number of transplant procedures/year, whether or not treatment was carried out at a university hospital, JACIE accreditation, and years of center experience in alloHCT in the respective year of HCT within the German health care system.

Statistical analysis

Descriptive statistics were presented for patient-, transplant- and center-related variables separately for patients transplanted in a center with <40 transplants per year (low volume centers) and those with ≥40 transplants per year (high volume centers). Absolute and relative numbers were reported for categorical variables, and mean and standard deviation for continuous variables. Allocation of the respective patients to either center with <40 and ≥40 allogeneic transplantation procedures per year was performed according to center volume in the respective year of HCT. Administrative censoring after one year follow-up post HCT was used for survival analysis in order to keep the dataset homogeneous. In addition, identical analyses were carried out without administrative censoring. OS, event-free survival (EFS) (event defined as relapse, progression or death) and the competing risks of relapse/progression and non-relapse/progression mortality (NRM) were assessed in both univariable and multivariable analyses. In addition to center size (<40 *vs.* ≥40), age, gender, disease status at alloHCT, graft source, donor type, conditioning, Karnofsky Index, HCT-specific Comorbidity Index (HCT-CI), European LeukemiaNet AML Risk (ELN), university status, center experience, and JACIE accreditation were considered. Cox proportional hazards models (likelihood ratio test) were calculated for OS and EFS, and Fine & Gray models for competing risks (univariable and multivariable, respectively). The Kaplan-Meier method and the log-rank test was used for univariable OS and EFS analysis of the impact of center size, and the Aalen-Johansen estimator and the Gray test for competing risk analysis. For multivariable analysis, best subset selection with Akaike information criterion (AIC) was calculated to determine the optimal set of variables. For sensitivity analysis, center size cut-offs were set at each possible value, and both univariable and multivariable analyses were calculated for all endpoints using these cut-off points. Hazard Ratios were observed. An additional sensitivity analysis considered center size as

a continuous variable. As the relationship between center size and the observed outcomes is non-linear, it is not possible to include center size as a standard continuous variable in the multivariable model due to the assumption of linearity. Spline modelling via p-splines was used to account for this non-linear modeling.[9]

Results

Patients' characteristics

A total of 5,328 consecutive patients treated in 52 German centers performing alloHCT and reporting to the DRST during the index period were included (Table 1). Median age was 58 years (range: 18-83). 56% of patients were male. 52% of patients were documented in first CR, and 45% had a more advanced disease status at HCT. In 95% of the patients, peripheral blood stem cells were used as graft source and bone marrow in the remainder. A total of 1,549 (20%) patients were transplanted from an HLA-matched related (MRD), and 2,595 (49%) from a matched (10/10 HLA match) unrelated donor (MUD). 592 (11%) patients each were transplanted from a mismatched related donor (MMRD), i.e., a haploidentical, and a mismatched (9/10 HLA-match) unrelated donor (MMUD), respectively. Donor source was balanced between high volume (≥40 HCT/year) and low volume (<40 HCT/year) centers apart from a slightly higher number of MRD among the low volume centers. Low volume centers had more patients with favorable performance status and HCT-CI (with HCT-CI score often missing), respectively, and used myeloablative conditioning (MAC) more frequently. High volume centers more often had >10 years center experience, were university hospitals, and were JACIE accredited.

Outcome

Kaplan-Meier-estimated OS and EFS rates at 12 months were 65.8% (95% Confidence Interval (95%CI) [62.7%; 69.1%]) for patients transplanted in a center with <40 HCT/year and 71.1% [69.7%; 72.5%] in a center with ≥40 HCT/year (P=0.0004, by log-rank test), and 57.5% [54.1%; 61.0%] and 61.5% [60.0%; 63.1%] [P=0.0112], respectively (Figure 1).

Table 1. Patients' characteristics.

Variable	Group	<40 HCT/year N=893 (16.8%)	≥40 HCT/year N=4,435 (83.2%)
Age, mean (SD)	-	54.9 (13.07)	55.57 (13.02)
Gender, N (%)	Male	507 (56.8)	2,460 (55.5)
	Female	386 (43.2)	1,969 (44.4)
	Unknown	-	6 (0.1)
Disease status at Tx, N (%)	CR	472 (52.9)	2,317 (52.2)
	Not CR1	400 (44.8)	2,020 (45.5)
	Unknown	21 (2.4)	98 (2.2)
Graft, N (%)	PB	847 (94.8)	4,206 (94.8)
	BM	41 (4.6)	215 (4.8)
	CB	1 (0.1)	2 (0.0)
	Unknown	4 (0.4)	12 (0.3)
Donor, N (%)	MRD	312 (34.9)	1,237 (27.9)
	MMRD	99 (11.1)	493 (11.1)
	MMUD	95 (10.6)	497 (11.2)
	MUD	387 (43.3)	2,208 (49.8)
Conditioning, N (%)	MAC	645 (72.2)	1,980 (44.6)
	Non-MAC	236 (26.4)	2,232 (50.3)
	Unknown	12 (1.3)	223 (5.0)
Karnofsky Index, N (%)	90/100	630 (70.5)	2,542 (57.3)
	70/80	186 (20.8)	1,444 (32.6)
	10-60	24 (2.7)	140 (3.2)
	Unknown	53 (5.9)	309 (7.0)

Continued on following page.

Variable	Group	<40 HCT/year N=893 (16.8%)	≥40 HCT/year N=4,435 (83.2%)
University hospital, N (%)	Yes	458 (51.3)	4,338 (97.8)
	No	435 (48.7)	97 (2.2)
HCT-CI, N (%)	0-2	570 (63.8)	2,479 (55.9)
	3-10	233 (26.1)	1,154 (26)
	Missing	90 (10.1)	802 (18.1)
ELN, N (%)	Adverse	274 (30.7)	1,281 (28.9)
	BPDCN	8 (0.9)	22 (0.5)
	Favorable	129 (14.4)	690 (15.6)
	Intermediate	269 (30.1)	1,489 (33.6)
	Unknown	213 (23.9)	953 (21.5)
Center experience, N (%)	≥10 years	592 (66.3)	4,206 (94.8)
	5-10 years	228 (25.5)	193 (4.4)
	<5 years	73 (8.2)	36 (0.8)
JACIE, N (%)	Yes	369 (41.3)	3,517 (79.3)
	No	524 (58.7)	918 (20.7)

BM: bone marrow; BPDCN: blastic plasmacytoid dendritic cell neoplasm; CB: cord blood; CR: complete remission; CR1: 1st CR; ELN: European LeukemiaNet Classification; HCT-CI: Hematopoietic Cell Transplantation-Comorbidity Index; HCT/Tx: hematopoietic cell transplantation; JACIE: Joint Accreditation Committee ISCT-Europe & European Group for Blood and Marrow Transplantation (EBMT); MAC: myeloablative conditioning; MMRD: mismatched related donor; MMUD: mismatched unrelated donor; MRD: matched related donor; MUD: matched unrelated donor; N: number; PB: peripheral blood; SD: Standard Deviation; Tx: treatment.

Cumulative incidence of the competing risks of relapse/progression and NRM estimated at 12 months were 24.2% [21.3%; 27.2%] in centers with <40 HCT/year and 22.9% [21.6%; 24.3%] in centers with ≥40 HCT/year (*P*=0.569, by Gray test) and 18.4% [15.8%; 21.1%] and 15.5% [14.4%; 16.7%] [*P*=0.047], respectively (Figure 2).

On univariable analysis, center-specific predictors of an adverse OS (Table 2) were center size, measured in number of HCT in the year of HCT <40 *versus* ≥40 (HR, 95% CI: 1.26 [1.11; 1.43]; *P*<0.001), university hospital no *versus* yes (1.30 [1.11; 1.53]; *P*=0.001), center experience 5-10 years and <5 years *versus* ≥10 years (1.26 [1.06; 1.50]; *P*=0.010 and 1.22 [0.87; 1.72]), whereas JACIE accreditation had no significant effect (1.02 [0.91; 1.15]; *P*=0.744). Patient- and disease-specific factors were also analyzed in the univariable analysis and most of them (except gender and conditioning) were statistically significant with effect sizes similar to what have been reported before (Tables 2-5). Likewise, on univariable analysis of predictors for improved EFS (Table 3), the effects for center size HCT <40 *versus* ≥40 (1.16 [1.04; 1.31], *P*=0.011), university hospital no *versus* yes (1.20 [1.04; 1.38]; *P*=0.013), center experience 5-10 years and <5 years *versus* ≥10 years (1.13 [0.96; 1.33]; *P*=0.138 and 1.24 [0.93; 1.67]; *P*=0.150), and JACIE accreditation no *versus* yes (1.02 [0.92; 1.13]; *P*=0.714) were largely similar to OS (Table 2). The same accounts for NRM, whereas significant effects of the four structural parameters could not be proven for the endpoint relapse/progression (Tables 4 and 5).

On multivariable analysis, relevant center-specific predictors for improved OS were number of HCT/year in year of HCT <40 *versus* ≥40 (1.21 [1.02; 1.45]; *P*=0.032), university hospital no *versus* yes (1.21 [0.98; 1.49]; *P*=0.071), and center experience 5-10 years and <5 years *versus* ≥10 years (1.234 [1.020; 1.494]; *P*=0.031 and 1.063 [0.737; 1.532]; *P*=0.743), but not JACIE accreditation, which did not remain in the model after best subset selection. Patient- and disease-specific factors all remained in the model as relevant co-variates, with effects similar to those in the univariable analysis. Identical analyses without administrative censoring after one year follow-up post HCT for survival analysis yielded essentially similar results (*Online Supplementary Tables S1-S4*).

When the model determined for OS was calculated for the endpoints EFS and the competing events relapse/progression and NRM, the effects of center-specific factors were less strong compared to OS: center size HCT <40 *versus* ≥40 (EFS: 1.12 [0.96; 1.31], *P*=0.164; relapse/progression: 1.05 [0.85; 1.28], *P*=0.668; NRM: 1.23 [0.98; 1.56], *P*=0.080); university hospital no *versus* yes (1.13 [0.93; 1.36], *P*=0.218; 0.96 [0.76; 1.23], *P*=0.764; 1.26 [0.95; 1.66], *P*=0.109) and center experience 5-10 years and <5 *versus* ≥10 years (1.12 [0.94; 1.34], *P*=0.188 and 1.10 [0.80; 1.51], *P*=0.564; 1.23 [1.00; 1.53], *P*=0.054 and 0.92 [0.60; 1.41], *P*=0.701; 0.92 [0.70; 1.21], *P*=0.548 and 1.23 [0.80; 1.90], *P*=0.338). The impact of patient- and disease-specific factors is shown in the *Online Supplementary Tables S2-S4*.

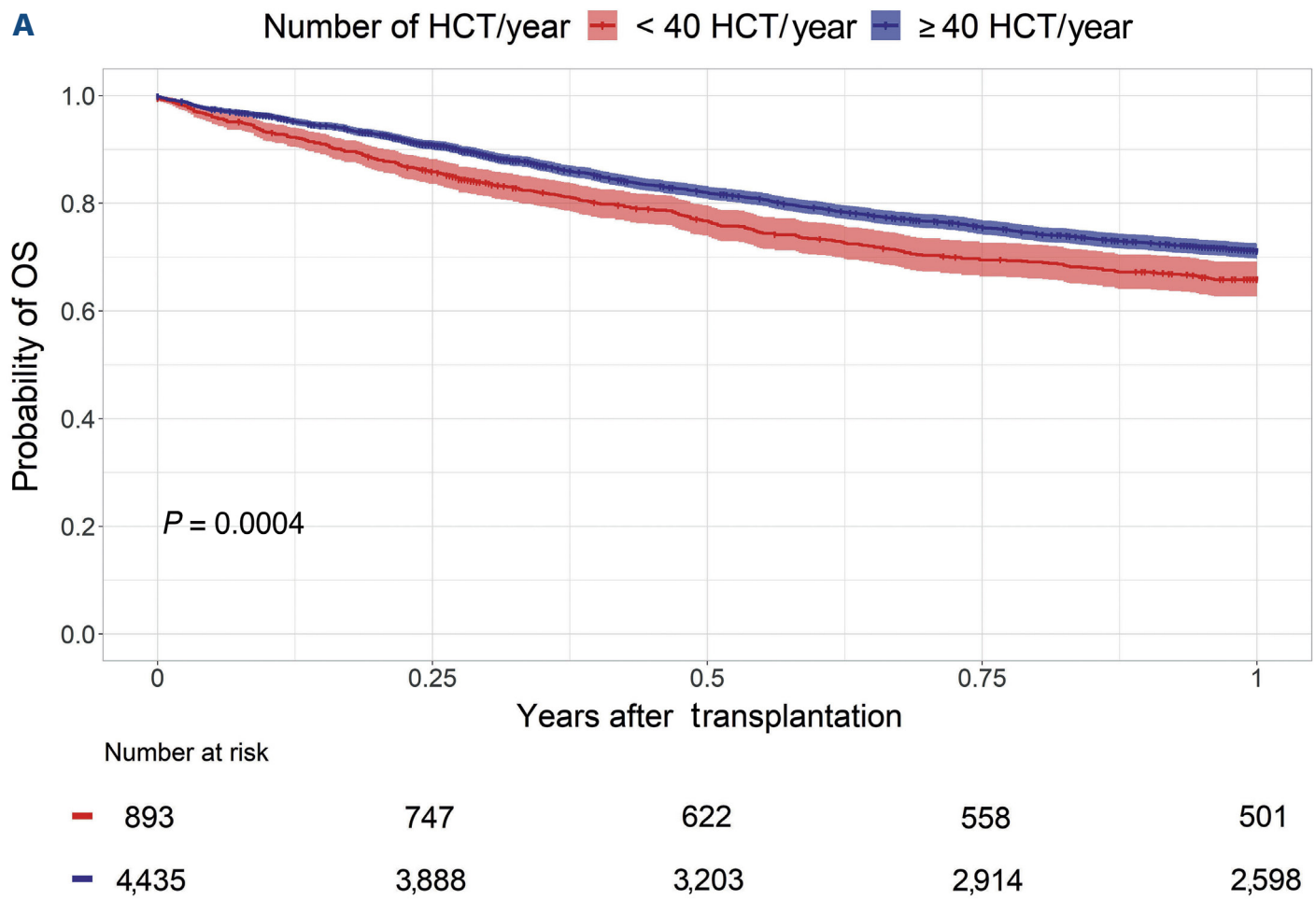

Figure 1. Kaplan-Meier plots of survival. (A) Overall survival. (B) Event-free survival.

Modeling of center size effect

In order to assess whether the significance of the predefined cut-off level of 40 HCT/center/year was not achieved by chance, we performed serial analyses of multivariable Cox regression and calculated adjusted HR and 95%CI for all cut-off points and plotted them. With this method, HR including CI were below 1 for all cut-off points between 30 and 70 HCT/year, whereas all other cut-off points had no

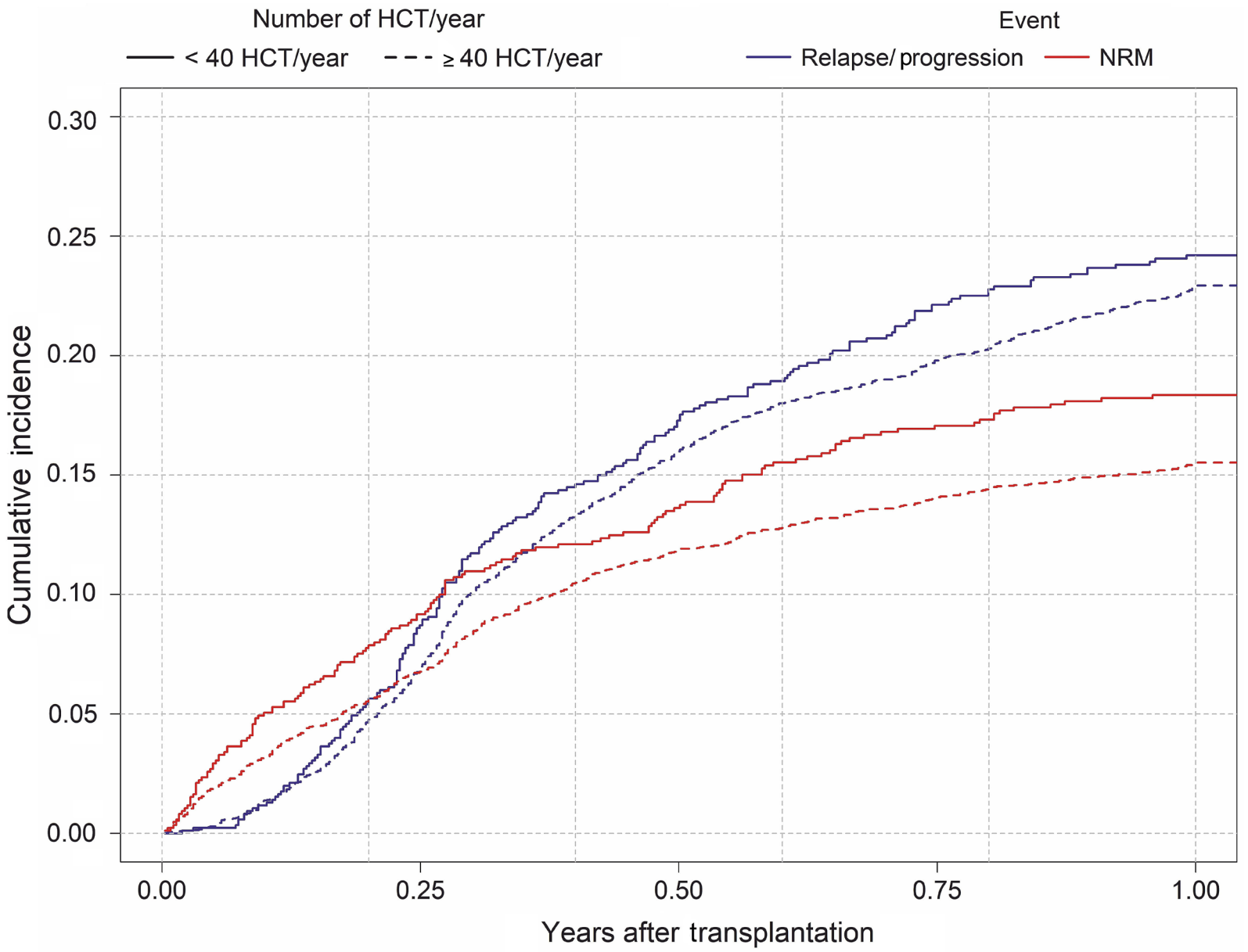

Figure 2. Cumulative incidence non-relapse mortality and relapse.

Table 2. Risk factor analysis overall survival.

Variable	Reference	Exposure	Univariable analysis HR (95% CI), *P* value	Multivariable analysis HR (95% CI), *P* value
Center size (HCT/year)	≥40	<40	1.260 (1.108-1.434), <0.001	1.212 (1.016-1.445), 0.032
University hospital	Yes	No	1.303 (1.112-1.527), 0.001	1.210 (0.984-1.488), 0.071
Center experience	≥10 years	5-10 years	1.260 (1.057-1.503), 0.010	1.234 (1.020-1.494), 0.031
		<5 years	1.223 (0.870-1.719), 0.247	1.063 (0.737-1.532), 0.743
JACIE	Yes	No	1.020 (0.907-1.146), 0.744	-
Age	Continuous	-	1.028 (1.023-1.033), <0.001	1.024 (1.019-1.029), <0.001
Gender	M	F	0.929 (0.837-1.031), 0.164	1.024 (0.919-1.141), 0.667
Karnofsky Index	90/100	70/80	1.569 (1.402-1.754), <0.001	1.368 (1.214-1.541), <0.001
		10-60	2.388 (1.880-3.034), <0.001	1.827 (1.428-2.337), <0.001
		Unknown	1.729 (1.435-2.084), <0.001	1.516 (1.222-1.881), <0.001
HCT-CI	0-2	3-10	1.407 (1.250-1.584), <0.001	1.201 (1.061-1.359), 0.004
		Unknown	1.484 (1.295-1.700), <0.001	1.380 (1.186-1.606), <0.001
ELN	Adverse	BPDCN	0.916 (0.474-1.770), 0.794	1.025 (0.527-1.992), 0.942
		Favorable	0.538 (0.451-0.642), <0.001	0.549 (0.457-0.659), <0.001
		Intermediate	0.715 (0.630-0.811), <0.001	0.786 (0.689-0.895), <0.001
		Unknown	0.768 (0.667-0.883), <0.001	0.710 (0.611-0.826), <0.001

Continued on following page.

Variable	Reference	Exposure	Univariable analysis HR (95% CI), *P* value	Multivariable analysis HR (95% CI), *P* value
Conditioning	MAC	Non-MAC	1.085 (0.977-1.205), 0.128	0.930 (0.829-1.043), 0.212
Disease status at Tx	CR1	Not CR1	2.149 (1.930-2.392), <0.001	1.985 (1.775-2.219), <0.001
Graft	PB	BM	1.368 (1.106-1.694), 0.004	1.203 (0.943-1.533), 0.136
Donor	MRD	MMRD	1.501 (1.265-1.782), <0.001	1.305 (1.080-1.577), 0.006
		MMUD	1.567 (1.325-1.854), <0.001	1.405 (1.178-1.675), <0.001
		MUD	1.053 (0.927-1.196), 0.424	0.974 (0.852-1.114), 0.705

BM: bone marrow; BPDCN: blastic plasmacytoid dendritic cell neoplasm; CB: cord blood; CI: Confidence Interval; CR: complete remission; CR1: 1st CR; ELN: European LeukemiaNet Classification; F: female; HCT-CI: Hematopoietic Cell Transplantation-Comorbidity Index; HCT/Tx: hematopoietic cell transplantation; HR: Hazard Ratio; JACIE: Joint Accreditation Committee ISCT-Europe & European Group for Blood and Marrow Transplantation (EBMT); M: male; MAC: myeloablative conditioning; MMRD: mismatched related donor; MMUD: mismatched unrelated donor; MRD: matched related donor; MUD: matched unrelated donor; PB: peripheral blood; Tx: treatment.

Table 3. Risk factor analysis event-free survival.

Variable	Reference	Exposure	Univariable analysis HR (95% CI), *P* value	Multivariable analysis HR (95% CI), *P* value
Center size (HCT/year)	≥40	<40	1.162 (1.035-1.306), 0.011	1.119 (0.955-1.310), 0.164
University hospital	Yes	No	1.200 (1.040-1.384), 0.013	1.125 (0.933-1.356), 0.218
Center experience	≥10 years	5-10 years	1.130 (0.962-1.329), 0.138	1.124 (0.944-1.339), 0.188
		<5 years	1.243 (0.925-1.671), 0.150	1.097 (0.800-1.506), 0.564
JACIE	Yes	No	1.019 (0.920-1.129), 0.714	-
Age	Continuous	-	1.012 (1.008-1.016), <0.001	1.009 (1.005-1.013), <0.001
Gender	M	F	0.936 (0.855-1.026), 0.158	0.978 (0.890-1.076), 0.650
Karnofsky Index	90/100	70/80	1.304 (1.181-1.440), <0.001	1.205 (1.085-1.338), 0.001
		10-60	1.840 (1.469-2.304), <0.001	1.499 (1.189-1.890), 0.001
		Unknown	1.519 (1.282-1.801), <0.001	1.435 (1.185-1.738), <0.001
HCT-CI	0-2	3-10	1.168 (1.051-1.299), 0.004	1.049 (0.939-1.172), 0.394
		Unknown	1.313 (1.163-1.481), <0.001	1.274 (1.115-1.455), <0.001
ELN	Adverse	BPDCN	0.760 (0.407-1.420), 0.390	0.858 (0.458-1.609), 0.634
		Favorable	0.575 (0.494-0.670), <0.001	0.564 (0.481-0.660), <0.001
		Intermediate	0.777 (0.696-0.867), <0.001	0.826 (0.737-0.926), 0.001
		Unknown	0.757 (0.667-0.858), <0.001	0.700 (0.612-0.800), <0.001
Conditioning	MAC	Non-MAC	1.040 (0.948-1.140), 0.407	0.972 (0.879-1.075), 0.580
Disease status at Tx	CR1	Not CR1	1.879 (1.714-2.061), <0.001	1.830 (1.662-2.015), <0.001
Graft	PB	BM	1.483 (1.232-1.785), <0.001	1.378 (1.119-1.696), 0.003
Donor	MRD	MMRD	1.214 (1.040-1.419), 0.014	1.056 (0.890-1.251), 0.533
		MMUD	1.360 (1.172-1.579), <0.001	1.260 (1.078-1.473), 0.004
		MUD	0.989 (0.887-1.103), 0.849	0.972 (0.867-1.090), 0.628

BM: bone marrow; BPDCN: blastic plasmacytoid dendritic cell neoplasm; CB: cord blood; CI: Confidence Interval; CR: complete remission; CR1: 1st CR; ELN: European LeukemiaNet Classification; F: female; HCT-CI: Hematopoietic Cell Transplantation-Comorbidity Index; HCT/Tx: hematopoietic cell transplantation; HR: Hazard Ratio; JACIE: Joint Accreditation Committee ISCT-Europe & European Group for Blood and Marrow Transplantation (EBMT); M: male; MAC: myeloablative conditioning; MMRD: mismatched related donor; MMUD: mismatched unrelated donor; MRD: matched related donor; MUD: matched unrelated donor; PB: peripheral blood; Tx: treatment.

Table 4. Risk factor analysis non-relapse mortality.

Variable	Reference	Exposure	Univariable analysis HR (95% CI), *P* value	Multivariable analysis HR (95% CI), *P* value
Center size (HCT/year)	≥40	<40	1.218 (1.022-1.451), 0.028	1.232 (0.975-1.556), 0.080
University hospital	Yes	No	1.311 (1.061-1.620), 0.012	1.255 (0.951-1.656), 0.109
Center experience	≥10 years	5-10 years	0.992 (0.765-1.287), 0.953	0.918 (0.695-1.213), 0.548
		<5 years	1.392 (0.905-2.140), 0.132	1.234 (0.803-1.896), 0.338
JACIE	Yes	No	1.045 (0.894-1.222), 0.581	-
Age	Continuous	-	1.038 (1.031-1.046), <0.001	1.033 (1.025-1.041), <0.001
Gender	M	F	0.998 (0.868-1.148), 0.977	1.074 (0.930-1.240), 0.328
Karnofsky Index	90/100	70/80	1.622 (1.396-1.885), <0.001	1.375 (1.174-1.611), <0.001
		10-60	2.661 (1.974-3.586), <0.001	2.083 (1.536-2.825), <0.001
		Unknown	1.493 (1.136-1.960), 0.004	1.440 (1.067-1.943), 0.017
HCT-CI	0-2	3-10	1.607 (1.374-1.880), <0.001	1.346 (1.143-1.584), <0.001
		Unknown	1.432 (1.187-1.727), <0.001	1.377 (1.122-1.690), 0.002
ELN	Adverse	BPDCN	1.000 (0.426-2.348), 1.000	1.162 (0.509-2.653), 0.722
		Favorable	0.650 (0.513-0.824), <0.001	0.676 (0.530-0.863), 0.002
		Intermediate	0.874 (0.738-1.037), 0.122	0.987 (0.830-1.174), 0.886
		Unknown	0.875 (0.722-1.061), 0.174	0.870 (0.707-1.070), 0.186
Conditioning	MAC	Non-MAC	1.206 (1.047-1.388), 0.009	0.981 (0.840-1.146), 0.808
Disease status at Tx	CR1	Not CR1	1.935 (1.676-2.234), <0.001	1.719 (1.482-1.994), <0.001
Graft	PB	BM	1.124 (0.827-1.527), 0.455	0.978 (0.700-1.365), 0.894
Donor	MRD	MMRD	1.559 (1.237-1.964), <0.001	1.461 (1.136-1.880), 0.003
		MMUD	1.678 (1.341-2.098), <0.001	1.481 (1.174-1.868), 0.001
		MUD	1.108 (0.930-1.319), 0.251	0.978 (0.814-1.174), 0.810

BM: bone marrow; BPDCN: blastic plasmacytoid dendritic cell neoplasm; CB: cord blood; CI: Confidence Interval; CR: complete remission; CR1: 1st CR; ELN: European LeukemiaNet Classification; F: female; HCT-CI: Hematopoietic Cell Transplantation-Comorbidity Index; HCT/Tx: hematopoietic cell transplantation; HR: Hazard Ratio; JACIE: Joint Accreditation Committee ISCT-Europe & European Group for Blood and Marrow Transplantation (EBMT); M: male; MAC: myeloablative conditioning; MMRD: mismatched related donor; MMUD: mismatched unrelated donor; MRD: matched related donor; MUD: matched unrelated donor; PB: peripheral blood; Tx: treatment.

significant discriminative impact (Figure 3A).

To further define the ideal cut-off point of center size (which is a non-linear variable), spline modeling was performed (Figure 3B). HR and 95%CI for corresponding number of HCT/year in comparison to all other HCT numbers in multivariable analysis were plotted. For OS, 45 HCT procedures/year and for EFS, 48 HCT procedures/year were identified as the minimum center size without significantly higher hazards compared to other center sizes.

Discussion

Patient-, disease-, and procedure-specific factors influencing outcomes of allogeneic HCT have been extensively studied and reported. Factors such as age, comorbidities, disease risk, donor type and conditioning have been shown to significantly influence outcome, similar to observations in our cohort.[9-12] In contrast, there is a paucity of studies examining the impact of transplant center characteristics, such as center experience, volume of allogeneic HCT performed, whether treatment was carried out at a university hospital or not, and the existence of a certified quality management system on HCT outcome. The few analyses available are restricted to individual health care systems and are often based on relatively old data sets.[13-15] Most frequently, hospital procedure-specific volumes and service provider level have been proposed to have an important impact.[6,14,16] However, volume may also be just a surrogate marker for experience, structural factors, and quality measures. Recent analyses in the US and Japan have shown a significant impact of center volume and experience on HCT outcome.[8,17]

The data presented here analyze for the first time the influence of center volume in the context of other center-specific factors on the outcome of allogeneic HCT in

Table 5. Statistical analysis relapse/progression.

Variable	Reference	Exposure	Univariable analysis HR (95% CI), *P* value	Multivariable analysis HR (95% CI), *P* value
Center size (HCT/year)	≥40	<40	1.078 (0.927-1.255), 0.328	1.045 (0.854-1.280), 0.668
University hospital	Yes	No	1.055 (0.873-1.275), 0.580	0.963 (0.755-1.229), 0.764
Center experience	≥10 years	5-10 years	1.207 (0.988-1.474), 0.066	1.234 (0.997-1.529), 0.054
		<5 years	1.075 (0.732-1.578), 0.713	0.920 (0.600-1.410), 0.701
JACIE	Yes	No	0.991 (0.869-1.131), 0.899	-
Age	Continuous	-	0.994 (0.990-0.998), 0.007	0.993 (0.988-0.998), 0.003
Gender	M	F	0.904 (0.804-1.016), 0.090	0.920 (0.814-1.040), 0.182
Karnofsky Index	90/100	70/80	1.030 (0.904-1.173), 0.660	1.012 (0.882-1.162), 0.862
		10-60	1.099 (0.796-1.516), 0.567	0.960 (0.690-1.334), 0.807
		Unknown	1.385 (1.122-1.710), 0.002	1.237 (0.972-1.573), 0.084
HCT-CI	0-2	3-10	0.867 (0.751-0.999), 0.049	0.845 (0.728-0.982), 0.028
		Unknown	1.167 (1.001-1.360), 0.049	1.151 (0.973-1.363), 0.101
ELN	Adverse	BPDCN	0.645 (0.260-1.603), 0.346	0.700 (0.284-1.729), 0.440
		Favorable	0.588 (0.485-0.715), <0.001	0.557 (0.455-0.682), <0.001
		Intermediate	0.754 (0.655-0.867), <0.001	0.766 (0.662-0.886), <0.001
		Unknown	0.723 (0.616-0.849), <0.001	0.662 (0.557-0.786), <0.001
Conditioning	MAC	Non-MAC	0.925 (0.822-1.042), 0.199	0.985 (0.868-1.117), 0.809
Disease status at Tx	CR1	Not CR1	1.576 (1.402-1.772), <0.001	1.634 (1.446-1.847), <0.001
Graft	PB	BM	1.640 (1.312-2.051), <0.001	1.630 (1.264-2.100), <0.001
Donor	MRD	MMRD	0.958 (0.780-1.177), 0.681	0.804 (0.641-1.009), 0.060
		MMUD	1.082 (0.890-1.315), 0.430	1.065 (0.866-1.308), 0.551
		MUD	0.921 (0.803-1.055), 0.235	0.979 (0.848-1.131), 0.776

BM: bone marrow; BPDCN: blastic plasmacytoid dendritic cell neoplasm; CB: cord blood; CI: Confidence Interval; CR: complete remission; CR1: 1st CR; ELN: European LeukemiaNet Classification; F: female; HCT-CI: Hematopoietic Cell Transplantation-Comorbidity Index; HCT/Tx: hematopoietic cell transplantation; HR: Hazard Ratio; JACIE: Joint Accreditation Committee ISCT-Europe & European Group for Blood and Marrow Transplantation (EBMT); M: male; MAC: myeloablative conditioning; MMRD: mismatched related donor; MMUD: mismatched unrelated donor; MRD: matched related donor; MUD: matched unrelated donor; PB: peripheral blood; Tx: treatment.

adult patients within the German health care system using a large recent (2015-2021) data set. To allow a homogeneous analysis while minimizing other confounding factors we decided to focus on AML as the major indication for adult allogeneic HCT. Apart from excluding pediatric patients and those receiving cord blood or <9/10 mismatched unrelated donor transplants, eligibility was unrestricted in terms of age, performance status, comorbidity, ELN risk, disease status, donor type, graft source, and transplant strategy in order to reflect the whole risk spectrum associated with AML allotransplants in adults. Our study discloses differences in patient selection according to the center size. Patients transplanted at high volume centers more often had a reduced Karnofsky Index and were more often transplanted from an unrelated donor.

Similar to previous studies, our analysis confirmed a positive impact of center volume on survival.[9,17-19] Giebel *et al.* found in an EBMT study on 1,413 patients with AML treated with reduced intensity conditioning (RIC) alloHCT an adverse effect of an annual RIC transplant rate of 15 or less on PFS, which was largely NRM-driven. Beyond 15 transplants per year they did not observe significant outcome effects of increasing numbers, but only few patients had been transplanted in centers performing more than 50 transplants per year.[18] Similarly, a recent large Japanese study reported reduced survival (HR 1.31 [1.2; 1.44]) associated with an annual transplant rate of 9.3 or less after alloHCT for AML, and also a second cut-off point at 32/year disclosed a significant OS disadvantage (HR 1.11 [1.03; 1.2]) for the intermediate volume group (9.1-32 allotransplants per year) compared to the centers with higher annual volumes.[17] In contrast to the present study and also to the Giebel study, in the Japanese series, the center effect was largely driven by relapse rather than NRM.

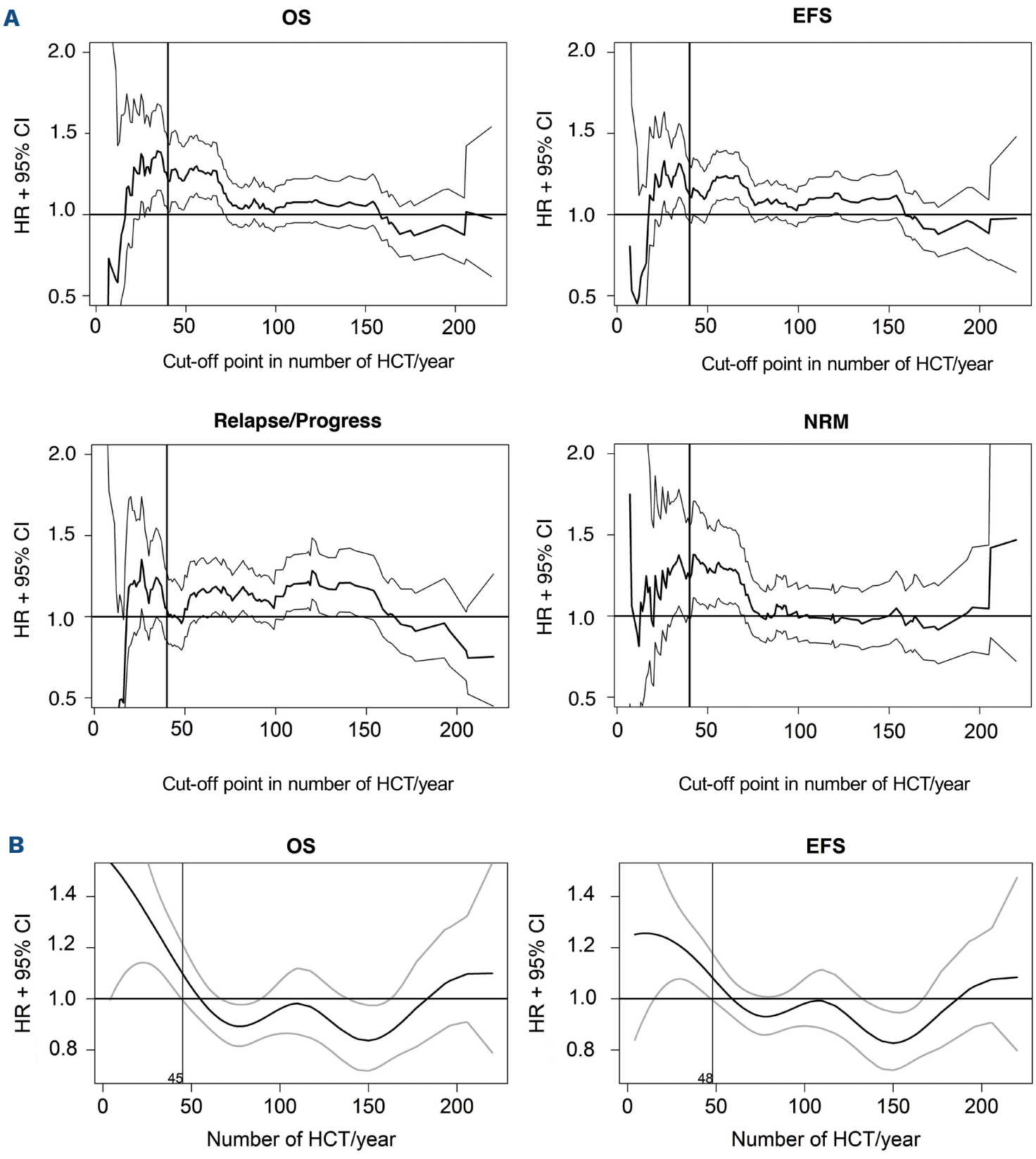

Figure 3. Multivariable analysis of Hazard Ratio and 95% Confidence Interval for all cut-off points. (A) Center size as non-linear variable. (B) Evaluation by Spline modeling. Hazard Ratio (HR) and 95% Confidence Interval (CI) for corresponding number of hematopoietic cell transplantation (HCT)/year in comparison to all other HCT numbers in multivariate analysis. EFS: event-free survival; NRM: non-relapse/progression mortality; OS: overall survival.

Of note, with an HR of 1.12 [0.96; 1.31] on multivariable analysis, in our sample, the center effect was smaller for EFS than for OS, suggesting that the observed survival benefit associated with high volume centers was partly due to superior outcome after post-transplant failure.

A unique added value of our study is that we were able to identify for the first time a minimum ideal cut-off point for the center effect. Although on multivariable Cox modeling each individual cut-off point between 30 and 70 alloHCT per year showed a survival advantage in the centers above the cut-off point compared to those below, spline modeling suggested a significant negative effect of each center volume below 45 allotransplants per year compared to all other center sizes. In comparison, center volumes of 45 or higher were not significantly worse than all other center sizes, implying that a significant OS benefit of further increasing the cut-off point does not become apparent beyond 45 allotransplants per year.

These findings are in keeping with a recent CIBMTR analysis by Majhail *et al.* where center transplantation volumes >40 alloHCT/year and presence of a survivorship program dedicated to HCT recipients were associated with supe-

rior OS.[8] However, as already discussed by Majhail *et al.*, one has to caution against using our threshold as the only benchmark for qualifying individual centers for alloHCT. The survival difference between the two center volume categories was relatively small, and center volume is only one factor among multiple structural parameters driving alloHCT outcome. Other center-specific factors predicting favorable survival in our analysis were university hospital status and program duration >5-10 years, the latter being in line with a previous analysis of the EBMT.[5] The same EBMT analysis reported a modest, NRM-driven effect of running an accredited QM system on OS,[5] a finding which could not be reproduced in the present analysis nor in the Majhail study.[8] However, nearly 80% of the high-volume centers in our study were also JACIE-accredited.

Using center volume as sole benchmark for quality of patient care also potentially ignores the important aspect of center accessibility and proximity to allow close follow up for the patient. The study of Majhail *et al.* already highlighted the importance of a survivorship and structured long-term follow-up program. At least half of the treatment-related mortality of allogeneic HCT occurs beyond day 100 after HCT.[19] A number of guidelines and recommendations exist for a specific long-term follow-up program after allogeneic HCT.[20] Unfortunately, we had no information on long-term follow-up programs and structures within our data set.

Being a retrospective registry report, our study has several limitations. There is certainly heterogeneity in patient selection across various centers. Data quality and granularity suffers from the retrospective nature of data collection. On the other hand, particular strengths of this analysis consist in the large sample size, enabling informative risk factor analyses, and in the comprehensive coverage of the German SOC HCT activity, with almost all qualified centers contributing data. However, before being generalized, our data need to be validated in other healthcare systems and in other alloHCT indications. In this context, it will be important to explore if alloHCT experience has a disease-specific component which over-rides the general allotransplant expertise, as has been reported for less common indications.[21]

Taken together, this analysis suggests that in adult patients with AML, in the German health care system the structural parameters of center volume, center experience, and university hospital status have a modest effect of almost similar impact on survival after alloHCT. The benefit of higher center volumes can be shown for each individual cut-off below 45 allotransplants per year. Validation of these findings in other allotransplant settings and health systems is warranted. These findings support efforts to centralize highly specialized therapeutic interventions such as alloHCT in experienced large volume, high-end care centers. However, healthcare planning has to simultaneously ensure easy patient access to alloHCT services also in less populated regions. This could possibly be achieved by establishing decentralized network structures, including regional long-term follow-up hubs, and modern telemedicine approaches.

Disclosures

No conflicts of interest to disclose.

Contributions

WB and PD designed the research, collected and analyzed data, and wrote the manuscript. SF designed the research, analyzed data, and wrote the manuscript. FH is responsible for data management. CS, MR, SK and JS designed the research and collected patient data. BH, MS, TS, IB, FA, ME and RZ collected patient data. KF and NK supervised data protection. All authors reviewed the manuscript.

Data-sharing statement

Original analysis data and protocols of this paper may be available to other investigators by request to the DRST (support@drst.de).

References

1. Lee SJ, Astigarraga CC, Eapen M, et al. Variation in supportive care practices in hematopoietic cell transplantation. Biol Blood Marrow Transplant. 2008;14(11):1231-1238.
2. Lee SJ, Joffe S, Artz AS, et al. Individual physician practice variation in hematopoietic cell transplantation. J Clin Oncol. 2008;26(13):2162-2170.
3. Pidala J, Lee SJ, Quinn G, Jim H, Kim J, Anasetti C. Variation in management of immune suppression after allogeneic hematopoietic cell transplantation. Biol Blood Marrow Transplant. 2011;17(10):1528-1536.
4. Trifilio S, Verma A, Mehta J. Antimicrobial prophylaxis in hematopoietic stem cell transplant recipients: heterogeneity of current clinical practice. Bone Marrow Transplant. 2004;33(7):735-739.
5. Gratwohl A, Sureda A, Baldomero H, et al. Economics and outcome after hematopoietic stem cell transplantation: a retrospective cohort study. EBioMedicine. 2015;2(12):2101-2109.
6. Gruen RL, Pitt V, Green S, Parkhill A, Campbell D, Jolley D. The effect of provider case volume on cancer mortality: systematic review and meta-analysis. CA Cancer J Clin. 2009;59(3):192-211.
7. Klingebiel T, Cornish J, Labopin M, et al. Results and factors influencing outcome after fully haploidentical hematopoietic stem cell transplantation in children with very high-risk acute lymphoblastic leukemia: impact of center size: an analysis on behalf of the Acute Leukemia and Pediatric Disease Working Parties of the European Blood and Marrow Transplant group. Blood. 2010;115(17):3437-3446.
8. Majhail NS, Mau LW, Chitphakdithai P, et al. Transplant center

characteristics and survival after allogeneic hematopoietic cell transplantation in adults. Bone Marrow Transplant. 2020;55(5):906-917.
9. Ayuk F, Beelen DW, Bornhauser M, et al. Relative impact of HLA matching and non-HLA donor characteristics on outcomes of allogeneic stem cell transplantation for acute myeloid leukemia and myelodysplastic syndrome. Biol Blood Marrow Transplant. 2018;24(12):2558-2567.
10. Fasslrinner F, Schetelig J, Burchert A, et al. Long-term efficacy of reduced-intensity versus myeloablative conditioning before allogeneic haemopoietic cell transplantation in patients with acute myeloid leukaemia in first complete remission: retrospective follow-up of an open-label, randomised phase 3 trial. Lancet Haematol. 2018;5(4):e161-e169.
11. Jentzsch M, Bischof L, Ussmann J, et al. Prognostic impact of the AML ELN2022 risk classification in patients undergoing allogeneic stem cell transplantation. Blood Cancer J. 2022;12(12):170.
12. Sorror ML, Appelbaum FR. Risk assessment before allogeneic hematopoietic cell transplantation for older adults with acute myeloid leukemia. Expert Rev Hematol. 2013;6(5):547-562.
13. Frassoni F, Labopin M, Powles R, et al. Effect of centre on outcome of bone-marrow transplantation for acute myeloid leukaemia. Acute Leukaemia Working Party of the European Group for Blood and Marrow Transplantation. Lancet. 2000;355(9213):1393-1398.
14. Loberiza FR Jr, Zhang MJ, Lee SJ, et al. Association of transplant center and physician factors on mortality after hematopoietic stem cell transplantation in the United States. Blood. 2005;105(7):2979-2987.
15. Mesnil F, Jouet J-P, Tuppin P, Vernant J-P, Golmard J-L. Evaluation of centre and period effects in allogeneic haematopoietic stem cell transplantation in France. Bone Marrow Transplant. 2004;34(7):645-651.
16. Choudhry NK, Fletcher RH, Soumerai SB. Systematic review: the relationship between clinical experience and quality of health care. Ann Intern Med. 2005;142(4):260-273.
17. Yanada M, Yano S, Kuwatsuka Y, et al. The effect of center experience on allogeneic hematopoietic cell transplantation outcomes in acute myeloid leukemia. Bone Marrow Transplant. 2024;59(4):541-549.
18. Giebel S, Labopin M, Mohty M, et al. The impact of center experience on results of reduced intensity: allogeneic hematopoietic SCT for AML. An analysis from the Acute Leukemia Working Party of the EBMT. Bone Marrow Transplant. 2013;48(2):238-242.
19. Brown RA, Adkins D, Khoury H, et al. Long-term follow-up of high-risk allogeneic peripheral-blood stem-cell transplant recipients: graft-versus-host disease and transplant-related mortality. J Clin Oncol. 1999;17(3):806-812.
20. Bhatia S. Caring for the long-term survivor after allogeneic stem cell transplantation. Hematology Am Soc Hematol Educ Program. 2014;2014(1):495-503.
21. Schetelig J, de Wreede LC, Andersen NS, et al. Centre characteristics and procedure-related factors have an impact on outcomes of allogeneic transplantation for patients with CLL: a retrospective analysis from the European Society for Blood and Marrow Transplantation (EBMT). Br J Haematol. 2017;178(4):521-533.