haematologica
Journal of the Ferrata Storti Foundation

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Received: May 21, 2026.
Accepted: August 25, 2026.

Citation: 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 and Peter Dreger. Allogeneic hematopoietic stem cell transplantation for acute myeloid leukemia: the association of JACIE accreditation/preparation and center volume.
Haematologica. 2026 Sept 3. doi: 10.3324/haematol.2026.301288 [Epub ahead of print]

Allogeneic hematopoietic stem cell transplantation for acute myeloid leukemia: the association of JACIE accreditation/preparation and center volume

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Keywords:
Hematopoietic Stem Cell Transplantation
Leukemia, Myeloid, Acute
Outcome Assessment, Health Care

Acknowledgments: We thank Alois Gratwohl for his valuable suggestions

Declarations: *Data availability statement:* not applicable; *Funding:* none

Compliance with ethical standards:
Conflict of interest: none
Research involving human participants and/or animals: not applicable
Informed consent: not applicable

Author's contributions: WB designed the research, collected and analyzed data, wrote manuscript, SF designed the research, analyzed data and wrote and reviewed manuscript, FH performed data management and reviewed manuscript, CS designed the research, collected patient data and reviewed manuscript, MR designed the research, collected patient data and reviewed manuscript, SK designed the research, collected patient data and reviewed manuscript, BH collected patient data and reviewed manuscript, JS designed the research, collected patient data and reviewed manuscript, MS collected patient data and reviewed manuscript, TS collected patient data and reviewed manuscript; IB collected patient data and reviewed manuscript, FA collected patient data and reviewed manuscript, ME collected patient data and reviewed manuscript, RZ collected patient data and reviewed manuscript, KF and NK supervised data protection and reviewed manuscript, PD designed the research, collected and analyzed data, wrote manuscript.

Authors' disclosures: The authors do not declare any conflicts of interest in relation to the manuscript above.
Supplemental figure: 1
Abstract: not applicable

To the editor

In our recent study on the impact of infrastructural parameters on survival after allogeneic hematopoietic stem cell transplantation (alloHCT) in patients with acute myeloid leukemia (AML), having installed a Joint Accreditation Committee ISCT-Europe & EBMT (JACIE) accredited quality assurance (QA) system seemed to have no relevant effect in addition to the variables center volume, center experience, and university hospital status[1]. In order to elucidate this unexpected finding, we have extended our analysis in two aspects. First, given the fact that in the pivotal studies[2,3] showing a positive effect of JACIE, not only actually granted JACIE accreditation, but also being in preparation or having applied for accreditation was associated with superior survival after alloHCT, we included the 3-year period preceding successful accreditation in addition to definite JACIE accreditation in our analysis. Second, to account for a potential correlation of JACIE accreditation/preparation with center volume, we analyzed its effect in centers performing less than 40 alloHCT per year vs. patients transplanted in higher-volume centers and, independently, across continuous center volumes. The results support the hypothesis that JACIE accreditation/preparation may have an independent beneficial survival effect in smaller volume centers that disappears with increasing center volume.

Survival differences between groups were estimated using the Kaplan–Meier method, with hazard ratios (HRs) and 95% confidence intervals calculated from univariable Cox regression. Competing risks were analyzed using cumulative incidence curves, and subdistribution hazard ratios were estimated using the Fine and Gray model. To evaluate effect modification by center volume, a mixed-effects Cox proportional hazards model was fitted, including JACIE status, center volume, and their interaction as fixed

effects, with center included as a random intercept. From these models, HRs across the range of center volumes and corresponding 95% confidence intervals were derived. Patient distributions were visualized using histograms stratified by center volume and JACIE accreditation status. The analyses were performed using the same patient sample as in the original study, consisting of 5,328 individuals with AML allotransplanted between 2015 and 2021 in 52 centers and registered with the DRST[1]. Endpoint was overall survival using administrative censoring at 12 months. 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).

Of the 4,435 patients treated in the higher-volume centers, 3,517 patients (79.3%) underwent alloHCT under JACIE accreditation, and 139 (3.1%) were treated in a center that received accreditation within the following 3 years. Among the 893 patients treated in centers with <40 annual alloHCT procedures, 369 (41.3%) were transplanted under JACIE accreditation, an additional 110 patients (12.3%) within the 3-year pre-accreditation corridor. Only 5 high-volume centers were neither JACIE accredited nor in preparation. Further details are summarized in **Table 1, Fig. Suppl. 1 and Table 1 Suppl.**.

When analyzing the effect of actual JACIE accreditation (yes vs. no), we did not observe a beneficial OS effect of JACIE accreditation (HR [95% CI]: 0.981 [0.872; 1.103], **Fig. 1A**). This result did not change after shifting the 3-year-pre-accreditation patients from the no accreditation to the accreditation group (0.951 [0.840; 1.078], **Fig. 1B**), although the difference increased slightly. In the high-volume center subgroup, there was also no advantage of JACIE accreditation or preparation compared to no accreditation (1.105 [0.941; 1.299], **Fig. 1C**). In contrast, in the small-volume center subgroup, univariable

analysis suggested a modest numerical OS benefit for JACIE accreditation or preparation compared to no accreditation nor preparation (0.830 [0.658;1.046]; **Fig. 1D**). However, as the 95% CI includes 1, this difference was not statistically significant at the 0.05 level. Competing-risk analysis of NRM, treating relapse as a competing event, showed the opposite pattern, suggesting that differences in NRM mainly accounted for the OS difference (Fig. 2 A+B). This suggests the observed trend rather reflects improved transplant care rather than differences in disease-related outcomes.

A mixed-effects Cox proportional hazards model with a random intercept for center was used to assess the interaction between JACIE status and center size while explicitly accounting for unmeasured between-center heterogeneity. This revealed an increasing OS benefit in smaller centers with JACIE accreditation (**Fig. 2C**), which was even more pronounced when centers in preparation for JACIE accreditation were also classified as accredited (**Fig. 2D**). This stronger separation reflects the larger estimated interaction effect after centers preparing for JACIE accreditation were classified as accredited. The parameter estimates for both of these models are shown in Table 2 Suppl.. On multivariable analysis including all confounders considered in the original study, JACIE status (accreditation + 3-year-preaccreditation) did not remain in the final model identified through the previously applied best subset selection.

Opposed to our original analysis which did not show any effect of accomplished JACIE accreditation in addition to center volume, center experience, and center academic status across all centers, the present study including also centers in preparation for accreditation in the “JACIE yes” group disclosed a (not statistically significant) trend toward an effect of “working towards JACIE” in smaller size centers: with a HR of 0.83 the benefit of JACIE accreditation including the preparation phase in the low-volume

centers is comparable to the effect size seen in the pivotal study laying the ground for introduction of the JACIE system in the European alloHCT community. In the 2011 EBMT study, the HRs for JACIE accredited and “applied for accreditation” for OS were 0.87 and 0.93, respectively, which was significant at the 0.05 level in that 10-fold larger sample[2,3].

However, in the present study population, which has been treated more than 15 years after the original JACIE validation cohort, the beneficial survival effect of JACIE accreditation including “intent-to-JACIE” appears to diminish with increasing center volume, suggesting that it is not formal accreditation what drives favorable outcomes in larger centers. Similarly, JACIE accreditation history was outperformed by center volume in a Belgian study on 2858 autologous transplants performed between 2007 and 2013[4].

Limitations of this study include its post-hoc character and that it is restricted to a single entity in a single European country. Also the number of centers not being JACIE accredited or in preparation for JACIE was limited, particularly among the high-volume centers. On the other hand, it relies on a large homogeneous and well-characterized sample treated during a recent period, and is one of the few studies providing evidence for benefit of a cellular therapy quality management system on a hard endpoint.

Taken together, our findings are hypothesis-generating and suggest that establishing a JACIE-conform QA system may partly compensate for outcome deficits associated with limited center experience in alloHCT. With increasing center volume it becomes more and more difficult to demonstrate an added value of JACIE accreditation on survival – in contrast to other infrastructural parameters such as program duration and academic status. Undoubtedly one reason for this could be that the JACIE initiative has sensitized

also larger centers for the necessity of implementing an effective QA system but without seeking formal accreditation for it. Nevertheless, given the resources absorbed by the accreditation process, the results of this study could have implications on parameters such as the length of re-accreditation intervals. Moreover, as QA accreditation programs tend to proliferate autonomously, our findings could help to develop QA validation systems away from aiming at controlling every uncertainty towards controlling those uncertainties which are likely to be relevant in the real world, and ideally can be proven by scientific evaluation.

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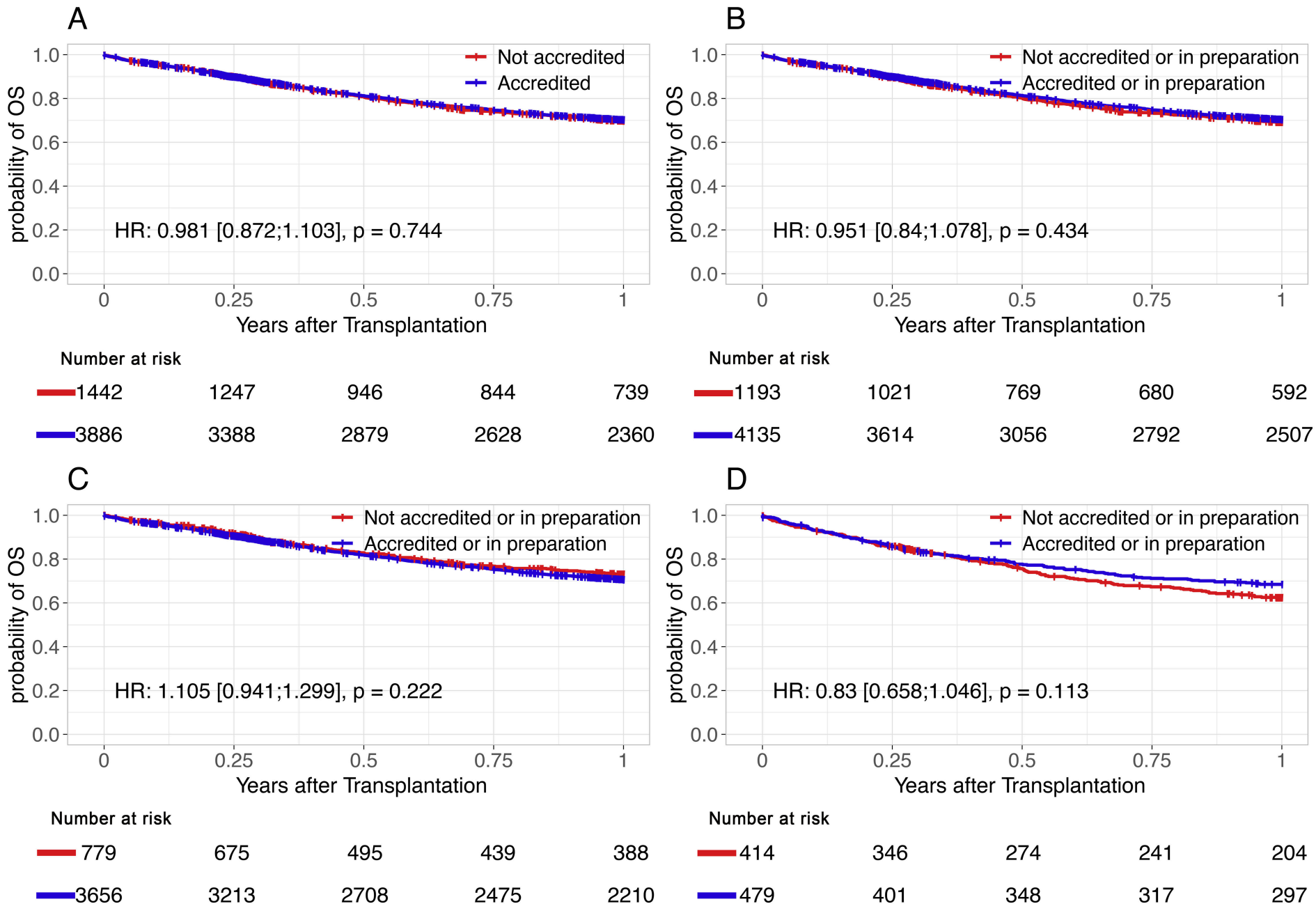
Table 1. Distribution of center-specific factors

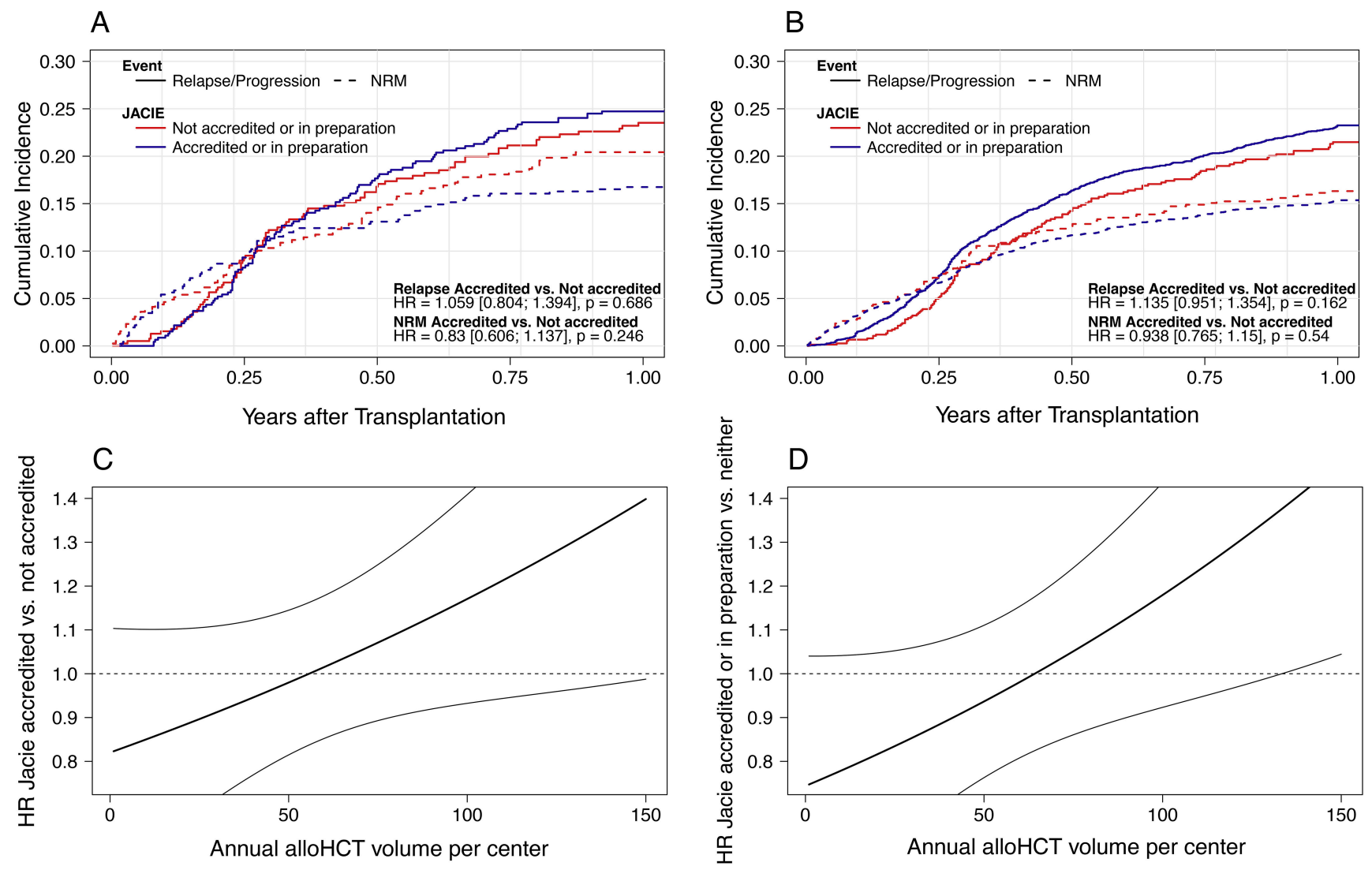
		JACIE		
		Accredited	In preparation	Neither
Annual alloHCT volume per center	≥40 alloHCT / year	3517 (79.3%)	139 (3.1%)	779 (17.6%)
	<40 alloHCT / year	369 (41.3%)	110 (12.3%)	414 (46.4%)
University status	Yes	3607 (75.2%)	198 (4.1%)	991 (20.7%)
	No	279 (52.4%)	51 (9.6%)	202 (38.0%)
Center experience	>10 years	3649 (76.1%)	147 (3.1%)	1002 (20.9%)
	5-10 years	235 (55.8%)	63 (15.0%)	123 (29.2%)
	<5 years	2 (1.8%)	39 (35.8%)	68 (62.4%)

Figures

Figure 1: Kaplan-Meier Survival estimates using univariate Cox regression A-D
A: all centers JACIE yes/no, **B**: all centers JACIE accredited or in preparation / neither, **C**: large centers JACIE accredited or in preparation / neither, **D**: small centers JACIE accredited or in preparation / neither

Figure 2: Cumulative incidence estimates and Fine & Gray model for competing risks Relapse/NRM E+F and Cox proportional hazards model analyzing differences in OS of the effect of JACIE status across center sizes G+H
A: NRM small centers: JACIE accredited or in preparation / neither; **B**: NRM large centers: JACIE accredited or in preparation / neither; **C**: OS HRs across the range of center volumes JACIE yes vs. no for, **D**: JACIE accredited or in preparation vs. neither.


A
Not accredited
Accredited
probability of OS
HR: 0.981 [0.872;1.103], p = 0.744
Years after Transplantation
Number at risk
1442 1247 946 844 739
3886 3388 2879 2628 2360
B
Not accredited or in preparation
Accredited or in preparation
probability of OS
HR: 0.951 [0.84;1.078], p = 0.434
Years after Transplantation
Number at risk
1193 1021 769 680 592
4135 3614 3056 2792 2507
C
Not accredited or in preparation
Accredited or in preparation
probability of OS
HR: 1.105 [0.941;1.299], p = 0.222
Years after Transplantation
Number at risk
779 675 495 439 388
3656 3213 2708 2475 2210
D
Not accredited or in preparation
Accredited or in preparation
probability of OS
HR: 0.83 [0.658;1.046], p = 0.113
Years after Transplantation
Number at risk
414 346 274 241 204
479 401 348 317 297


A
Event
Relapse/Progression
NRM
JACIE
Not accredited or in preparation
Accredited or in preparation
Relapse Accredited vs. Not accredited
HR = 1.059 [0.804; 1.394], p = 0.686
NRM Accredited vs. Not accredited
HR = 0.83 [0.606; 1.137], p = 0.246
Cumulative Incidence
Years after Transplantation
B
Event
Relapse/Progression
NRM
JACIE
Not accredited or in preparation
Accredited or in preparation
Relapse Accredited vs. Not accredited
HR = 1.135 [0.951; 1.354], p = 0.162
NRM Accredited vs. Not accredited
HR = 0.938 [0.765; 1.15], p = 0.54
Cumulative Incidence
Years after Transplantation
C
HR Jacie accredited vs. not accredited
Annual alloHCT volume per center
D
HR Jacie accredited or in preparation vs. neither
Annual alloHCT volume per center

Supplementary figures and tables

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Figure 1 Suppl. Distribution of center size by JACIE accreditation status. The figure shows the number of patients according to center size, stratified by JACIE status.

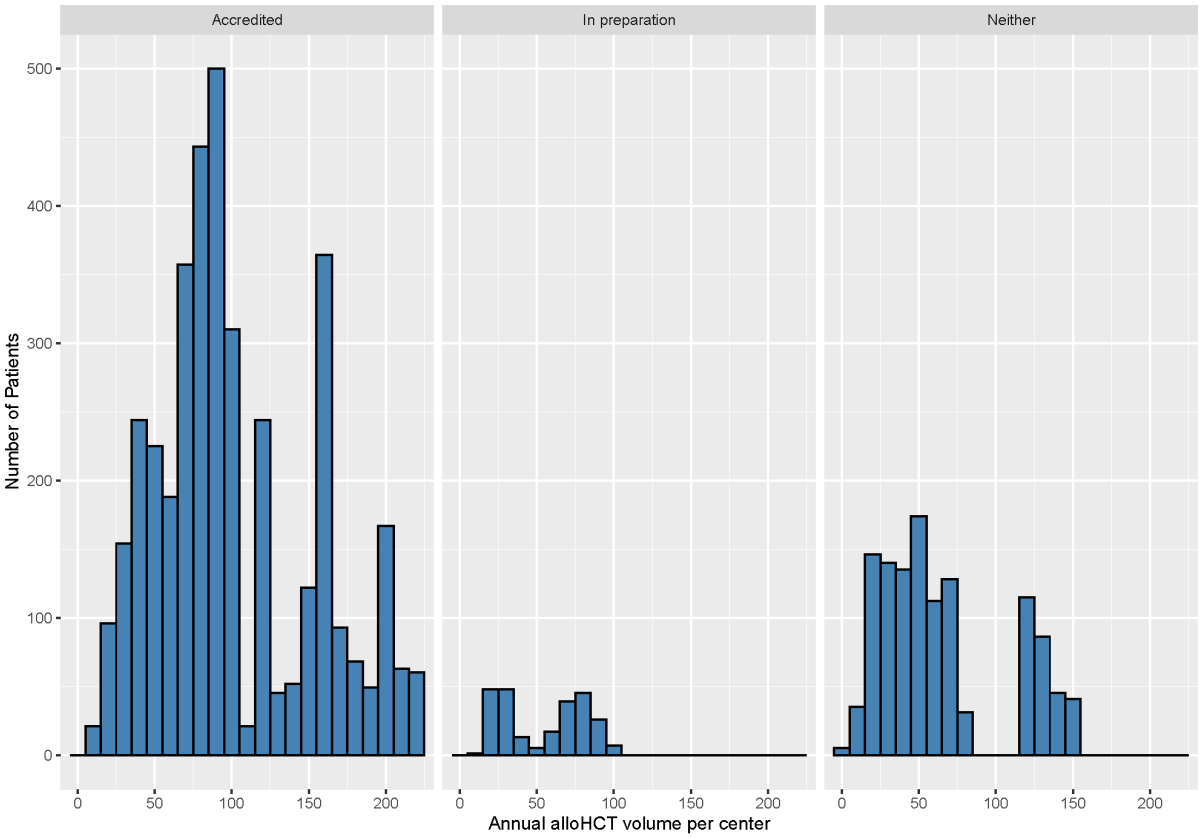

Table 1 Suppl.: Center category and JACIE during inclusion period

Important to note, center size, university status, center experience and Jacie accreditation or preparation status was determined in the year of HCT of the individual patient, a center could appear in more than one category, when its status changed over time (mixed group) as seen in this table.

		JACIE		
		Accredited or in preparation[a]	Mixed (Center changed from from [a] to [b] within the inclusion period)	Neither accredited nor in preparation[b]
Annual alloHCT volume per center	≥40 alloHCT / year	22	1	5
	<40 alloHCT / year	6	4	7
	Mixed (Center size varied during the inclusion period)	5	2	5
University status	Yes	28	3	9
	No	5	3	7
	Mixed (university status varied during the inclusion period)	0	1	1
Center experience	>10 years	27	0	12
	5-10 years			
	<5 years	0	1	1
	Mixed (Center experience varied during the inclusion period)	6	6	4

Table 2 Suppl.: Results of a mixed effect cox model

Variable	Model 1: disregarding the preparation phase	Model 2: considering the preparation phase
	HR [95% CI], p-value	
JACIE yes vs. no	0.820 [0.618; 1.089], 0.170	0.744 [0.553; 1.001], 0.050
Number allo Tx per year	0.995 [0.992; 0.999], 0.015	0.995 [0.991; 0.999], 0.007
interaction	1.004 [0.999; 1.008], 0.086	1.005 [1.000; 1.009] 0.036