

Introduction of a Quality Management System and Outcome After Hematopoietic Stem-Cell Transplantation

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A B S T R A C T

Purpose

A comprehensive quality management system called JACIE (Joint Accreditation Committee International Society for Cellular Therapy and the European Group for Blood and Marrow Transplantation), was introduced to improve quality of care in hematopoietic stem-cell transplantation (HSCT). We therefore tested the hypothesis that the introduction of JACIE improved patient survival.

Patients and Methods

Data on 41,623 allogeneic (39%) and 66,281 autologous (61%) HSCTs for an acquired hematologic disorder performed between 1999 and 2007 by 421 teams in Europe were used to assess the outcomes of patients who received a transplantation at baseline (> 3 years before application or no application), during preparation (3 years before application), during application (time from application to accreditation), and after JACIE accreditation. The analysis was clustered by team and stratified for year of HSCT, donor type, disease, conditioning, and gross national income per capita of the respective country. Patient's risks were adjusted for by their European Group for Blood and Marrow Transplantation score.

Results

Patient outcome was systematically better when the transplantation center was at a more advanced phase of JACIE accreditation, independent of year of transplantation and other risk factors. Improvement was robust as quantified for relapse-free survival after allogeneic HSCT compared with baseline by a hazard ratio (HR) of 0.96 (95% CI, 0.90 to 1.03; $P = .22$) for preparation, 0.95 (95% CI, 0.88 to 1.03; $P = .20$) for application, and 0.86 (95% CI, 0.78 to 0.95; $P = .01$) for the accreditation (test for trend $P = .01$). Improvement from baseline was similar after autologous HSCT (HR for accreditation, 0.83; 95% CI, 0.74 to 0.93; $P < .01$).

Conclusion

Even with all the limitations of an observational study, these findings support the hypothesis that introduction of a comprehensive clinical quality management system is associated with improved outcome of patients after HSCT.

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INTRODUCTION

Hematopoietic stem-cell transplantation (HSCT) is an established form of treatment for many patients with severe disorders of the hematopoietic system. The procedure is associated with substantial morbidity and mortality, and novel approaches to reduce its toxicity are warranted. Transplantation is a complex and expensive procedure, and it involves several independent groups, especially in the case of an unrelated donor transplantation.¹⁻⁶ Harmonization and standardization of the procedure have been advocated as way of improving patient care and outcome; thus, a comprehensive quality management

system has been developed.⁷ Accreditation for transplantation centers has become an accepted standard in Europe and the United States and is required by law in some countries. JACIE (The Joint Accreditation Committee International Society for Cellular Therapy Europe [ISCT] and the European Group for Blood and Marrow Transplantation [EBMT]) and its US counterpart, the Foundation for Accreditation of Cellular Therapy (FACT) are advanced quality management systems, the first of their kind in clinical medicine. The explicit aim was to improve quality of care in clinical HSCT by the use of well-defined standards, rules, and inspections. Implementation requires a substantial investment from

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transplantation teams.⁸ So far, there have not been any studies showing that these investments are justified by improving the patient outcome and that JACIE is not “just another cost-increasing exercise.”⁹

A reasonable time has passed since the introduction of JACIE, and a substantial number of teams have been accredited. The accreditation process evolved during that time, so now the effects of the different phases of the process can be assessed. In addition, EBMT has established a risk score to compare outcomes of mixed patient populations¹⁰ so an appropriate evaluation should be possible. Hence, the joint accreditation committee tested the hypothesis that improvement before, during, and after JACIE accreditation would exceed the baseline improvement over calendar time alone, independent of year of transplantation and other risk factors.

PATIENTS AND METHODS

Study Design

This retrospective analysis was based on the entire EBMT data set but was restricted to the window of time extending from 4 years before the first JACIE accreditation in Europe to January 1, 2007. The analysis therefore begins with January 1, 1999, the first calendar year in which at least one center started to work toward accreditation. The analysis was censored at the 3-year follow-up for all transplantations to achieve optimal comparability between all patients regardless of calendar year. The median survival among censored patients was 29 months; median survival of patients who died was 6.4 months. All EBMT teams were required to have the approval of their internal review board for their transplantation programs and to have their patients consent to data transfer.

Patient Population

Included in the final analysis were 107,904 patients (children and adults) with a first allogeneic ($n = 41,623$; 39%) or autologous ($n = 66,281$; 61%) HSCT for acute leukemia (27%), chronic leukemia (9%), lymphoma (34%), plasma cell disorder (24%), myelodysplastic syndromes and myeloproliferative syndromes (4%), or aplastic anemia (2%; Table 1). Median age was 48 years (range, 1 to 85 years); there were slightly more male patients (58.1% in allogeneic, 58.7% in autologous HSCT) than female patients. Approximately 30% of the patients had transplantations in early disease, 40% in intermediate-stage disease, and 20% in advanced-stage disease. Stem-cell sources were peripheral-blood stem cells for 74% of the allogeneic and for 97% of the autologous HSCTs.

Patients were categorized by the EBMT risk score, which includes disease stage (early, 0; intermediate, 1; advanced, 2; specifically defined for each disease separately), age of the patient (< 20 years, 0; 20 to 40 years, 1; > 40 years, 2), time interval from diagnosis to transplantation (< 12 months, 0; > 12 months, 1), donor type (HLA-identical sibling, 0; all others, 1), and sex combination (all other, 0; female donor for male recipient, 1). Hence, the scores ranged from 0 to 7 for allogeneic and from 0 to 5 for autologous HSCT.^{10,11}

JACIE Accreditation Status

Accreditation status was classified into four categories: baseline, preparation, application, and accreditation. This distinction was chosen on the postulation that if JACIE would have a true beneficial effect on outcome through quality improvement, a dose-response relationship could be expected with an improvement already in the preparation period.

About two thirds of the patients (75,704; 70%) were treated in a center that had not applied for JACIE accreditation at the time of transplantation for that particular patient; one third of the patients (32,200; 30%) received transplantation in centers that had applied for and/or received accreditation at the time of their transplantation. Patients who received transplantation by teams with no application or up to 36 months before application were included in the study with their JACIE covariate set as “baseline” (89,515; 83%); patients who received transplantations from 36 months up to the time of center application were classified as “in preparation” (11,689; 11%); patients who received trans-

plantations in a center between the date of its first application and the date of its accreditation were classified as “in application” (4,409; 4%); and patients who received transplantation after a center acquired its accreditation status were classified as “in accreditation” (2,291; 2%; Table 1). This JACIE variable served as a covariate to predict outcome at the patient level, not at the center level. This implies that all patients who received transplantation in one particular center in one particular calendar year shared the same value of this risk factor.

Statistical Analysis

The statistical models were kept as generic as possible, making as few assumptions as feasible, while accounting for the main confounders: disease, EBMT risk score, donor type, conditioning, calendar year, center, and gross national income per capita (GNI/capita) of the center’s country⁶ (data obtained from www.worldbank.org). The models focused on the four categories of accreditation status.

The framework chosen was the extended Cox proportional hazards model integrating cluster analysis.¹² Cause-specific hazards were calculated to cope with the competing risks of relapse and death. Disease and conditioning were considered as stratification factors, since survival of patients with different diseases was not proportional, as is shown in Figure 1 for allogeneic HSCT, and conditioning was not a target of the analysis. Therefore, the effect of JACIE accreditation status was estimated within each disease and averaged over the disease categories. All covariates were truly patient-level covariates, except for the JACIE status, which is shared among all patients who received transplantation in one particular center in one particular calendar year. The Cox models fitted to the data were clustered models, taking into account the center identification as cluster variable to ensure that the within-center correlation was taken into account. The models were not truly random-effect models since the effect of the JACIE accreditation was taken as a fixed factor, and center effects themselves were not estimated. The purpose of the analyses was not to estimate a center effect but to estimate a JACIE effect, taking a within-center clustering into account. The JACIE accreditation status was the only covariate (factor) operating at the center level; all other covariates were considered as patient and treatment characteristics. Hence, this procedure allowed us to measure the impact of the centers’ accreditation status on the outcomes of individual patients. Calendar year was introduced in all models as a factor, since proceeding through the various stages of accreditation was actually a calendar time process.

In addition, the effects of EBMT risk score and GNI/capita were assessed by introducing them as factors in the model, leaving all other risk factors as stratification factors, thus adjusting fully and with model assumptions for their various effects.

RESULTS

Population Description

There were significant changes over time. By definition, all patients received their transplantation in the baseline group or in the preparation phase in 1999; numbers of patients in the centers’ preparation, application, and accreditation phases steadily increased thereafter (Table 1). There was an increasing proportion of acute leukemia and a relative decrease in chronic leukemia over time, and there were significant differences between the different JACIE accreditation groups (Table 1). There was a steady increase in EBMT risk score from a median of 3.08 ± 1.27 for all HSCT, 2.98 ± 1.43 for allogeneic HSCT, and 3.15 ± 1.14 for autologous HSCT in 1999 to 3.24 ± 1.22 for all HSCT, 3.24 ± 1.52 for allogeneic HSCT, and 3.23 ± 0.98 for autologous HSCT in 2006. Centers with or without accreditation were of similar size. The proportion of teams in preparation, application, and accreditation status increased with increasing GNI/capita with no team in the lowest quartile of GNI/capita being accredited.

Table 1. Characteristics of Children and Adults With an Allogeneic (n = 41,623; 39%) or Autologous (n = 66,281; 61%) Transplantation

Characteristic	Phase Categories of JACIE Accreditation Process									
	Baseline		Preparation		Application		Accreditation		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%
Total No. of patients	89,515		11,689		4,409		2,291		107,904	
Sex										
Male	52,205	58.5	6,832	58.5	2,559	58.1	1,372	60.0	62,968	58.5
Female	37,081	41.5	4,846	41.5	1,842	41.9	915	40.0	44,684	41.5
First transplant type										
Allogeneic	33,753	37.7	4,890	41.8	1,922	43.6	1,058	46.2	41,623	38.6
Autologous	55,762	62.3	6,799	58.2	2,487	56.4	1,233	53.8	66,281	61.4
Donor relation										
Sibling	18,975	56.8	2,474	50.7	877	45.8	557	52.7	22,883	55.5
Syngeneic twin	294	0.9	37	0.8	14	0.7	8	0.8	353	0.9
Other family donor	2,349	7.0	222	4.5	96	5.0	42	4.0	2,709	6.6
Unrelated	11,792	35.3	2,150	44.0	928	48.5	450	42.6	15,320	37.1
Source of stem cells										
Bone marrow	14,854	17.2	1,674	14.6	588	13.6	324	14.9	17,440	16.7
Peripheral blood	71,752	82.8	9,787	85.4	3,721	86.4	1,848	85.1	87,108	83.3
Conditioning type										
Standard	47,053	52.6	6,963	59.6	2,383	54.0	1,291	56.4	57,690	53.5
Reduced	9,185	10.3	1,641	14.0	682	15.5	404	17.6	11,912	11.0
Missing	33,277	37.2	3,085	26.4	1,344	30.5	596	26.0	38,302	35.5
EBMT risk score										
0	2,141		183		92		43		2,459	
1	7,423		763		286		175		8,647	
2	16,492		2,224		731		478		19,925	
3	28,601		3,915		1,583		790		34,889	
4	22,624		2,912		1,097		520		27,153	
5	10,539		1,441		514		236		12,730	
6	1,560		233		96		41		1,930	
7	135		18		10		8		171	
Diagnosis										
Acute leukemia	24,096		3,298		1,327		763		29,484	
Chronic leukemia	8,123		1,047		335		147		9,652	
Lymphoma	30,951		3,761		1,227		573		36,512	
Plasma cell disorder	21,185		2,835		1,231		589		25,840	
MDS	3,293		564		205		137		4,199	
Aplastic anemia	1,867		184		84		82		2,217	
Calendar year										
1999	11,506	12.9	125	1.1	0	0.0	0	0.0	11,631	10.8
2000	11,698	13.1	330	2.8	13	0.3	0	0.0	12,041	11.2
2001	11,452	12.8	906	7.8	47	1.1	39	1.7	12,444	11.5
2002	11,524	12.9	1,561	13.4	15	0.3	125	5.5	13,225	12.3
2003	10,488	11.7	2,384	20.4	235	5.3	161	7.0	13,268	12.3
2004	10,563	11.8	2,508	21.5	969	22.0	175	7.6	14,215	13.2
2005	11,168	12.5	2,401	20.5	1,364	30.9	597	26.1	15,530	14.4
2006	11,116	12.4	1,474	12.6	1,766	40.1	1,194	52.1	15,550	14.4

NOTE. Characteristics of 107,904 patients with a hematopoietic stem-cell transplantation in Europe between 1999 and 2007 and Joint Accreditation Committee of the International Society for Cellular Therapy Europe and the European Group for Blood and Marrow Transplantation (JACIE) accreditation status of their transplantation teams. Numbers do not always add up because of missing values.

Abbreviations: EBMT, European Group for Blood and Marrow Transplantation; MDS, myelodysplastic syndromes.

Influence of EBMT Risk Score

Overall survival after allogeneic HSCT decreased systematically with increasing EBMT risk score¹⁰ from an HR of 1.0 (score 0+1) to 1.5 (score 2), 2.0 (score 3), 2.7 (score 4), and 3.3 (score 5 to 7) because of increasing nonrelapse mortality with increasing risk score from an HR of 1.0 (score 0+1) to 1.6 (score 2), 2.2 (score 3), 2.9 (score 4), and 3.8 (score 5 to 7). Similarly, overall survival after autologous HSCT decreased systematically with increasing EBMT risk score from an HR

of 1.0 (score 0+1) to 1.6 (score 2), 2.1 (score 3), 2.6 (score 4), and 3.4 (score 5) because of increasing nonrelapse mortality with increasing risk score from an HR of 1.0 (score 0+1) to 1.9 (score 2), 3.0 (score 3), 4.3 (score 4), and 5.8 (score 5).

GNI/Capita and Outcome

After allogeneic HSCT, overall survival as well as disease-free survival increased and nonrelapse mortality decreased systematically

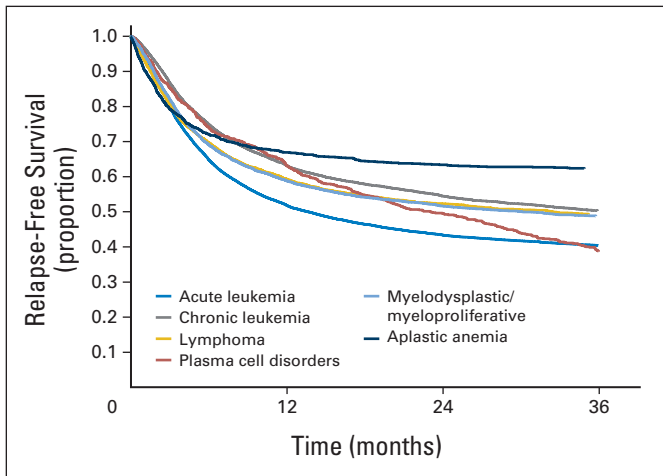


Fig 1. Relapse-free survival of 41,623 patients with an allogeneic hematopoietic stem-cell transplantation in Europe by main disease category.

with increasing GNI/capita as illustrated by an 8% increase in survival by quartile increase (robust trend test $P < .001$). There was no association with relapse rate (robust trend test $P = .19$) and no association after autologous HSCT.

JACIE Accreditation Status and Outcome

A systematic effect of JACIE accreditation status was observed (Table 2). HRs for both nonrelapse and relapse mortality decreased from baseline over the preparatory and application period up to the accreditation period. This effect translated into a significantly improved relapse-free survival for the patients who received transplantations in centers that were accredited when their transplantations took place. Results were robust and systematic in allogeneic patients. The effects were of the same order of magnitude for patients with

autologous HSCT between baseline and accreditation period but were not as systematic and robust.

Figure 2 presents the estimated average of the JACIE accreditation effect for patients with an intermediate EBMT risk score of 3 and a standard conditioning allogeneic transplantation in 2003 for chronic leukemia. It illustrates the systematic improvement with each step, adjusted for the calendar year and GNI/capita by stratification and by averaging over the strata. It shows an improvement in relapse-free survival of approximately 4% over baseline per accreditation step, resulting in an overall improvement of 14% (HR, 0.86).

To exclude the possibility that accredited centers represented an a priori selection of teams with better patient outcome, the analysis was repeated, and this time it was restricted to those centers that had gone through the whole accreditation process but at different points in calendar time. The analysis confirmed the same systematic stepwise improvement in patient outcome. Patients in these accredited centers had an approximately 2% better survival at baseline.

The effects of JACIE accreditation status remained the same when different modeling approaches were applied. When calendar year and risk score were analyzed as discrete covariates, HRs for the JACIE variable were affected only slightly, indicating that both risk score and calendar year had proportional impacts on patient outcome. Tests for interaction, including disease, EBMT risk score, conditioning, donor type, and the JACIE accreditation (as a continuous covariate) failed to show any interactions of accreditation status.

DISCUSSION

These data confirmed our hypothesis that outcome of patients after HSCT should be associated with JACIE accreditation status. Nonrelapse mortality, relapse incidence and, as a consequence, relapse-free survival after allogeneic HSCT were significantly and relevantly better

Table 2. Overall Survival, Relapse Incidence, Nonrelapse Mortality, and Relapse-Free Survival After HSCT in Europe in Association With JACIE Accreditation of the Respective Transplantation Team

Accreditation Categories*	Overall Survival			Relapse Incidence			Nonrelapse Mortality			Relapse-Free Survival		
	HR	95% CI	P†	HR	95% CI	P†	HR	95% CI	P†	HR	95% CI	P†
Allogeneic HSCT												
Baseline	1			1			1			1		
Preparation	0.98	0.91 to 1.04	.48	0.99	0.91 to 1.07	.75	0.93	0.84 to 1.03	.16	0.96	0.90 to 1.03	.22
Application	0.93	0.86 to 1.00	.07	0.95	0.84 to 1.07	.39	0.95	0.84 to 1.07	.41	0.95	0.88 to 1.03	.20
Accreditation	0.87	0.79 to 0.97	.01	0.83	0.72 to 0.96	.01	0.89	0.77 to 1.02	.09	0.86	0.78 to 0.95	.01
Average/phase	0.96	0.93 to 0.99	.02	0.96	0.92 to 1.00	.09	0.96	0.92 to 1.01	.09	0.96	0.93 to 0.99	.01
Autologous HSCT												
Baseline	1			1			1			1		
Preparation	1.01	0.93 to 1.11	.76	1.00	0.92 to 1.09	1.00	0.90	0.83 to 1.18	.90	1.00	0.93 to 1.07	.96
Application	1.02	0.90 to 1.17	.71	1.01	0.91 to 1.12	.83	0.94	0.73 to 1.21	.63	1.00	0.91 to 1.09	.98
Accreditation	0.90	0.73 to 1.11	.32	0.82	0.73 to 0.93	< .01	0.85	0.57 to 1.26	.42	0.83	0.74 to 0.93	< .01
Average/phase	0.99	0.94 to 1.05	.82	0.98	0.94 to 1.02	.29	0.96	0.87 to 1.07	.48	0.97	0.94 to 1.01	.18

NOTE. Data represent HRs adjusted for all other risk factors by stratification. "Average/phase" denotes the average HR when moving from one category to the next. The associated P value refers to the robust score (log-rank test; corrected test for trend).

Abbreviations: HSCT, hematopoietic stem-cell transplantation; JACIE, Joint Accreditation Committee of the International Society for Cellular Therapy Europe and the European Group for Blood and Marrow Transplantation; HR, hazard ratio.

*Phase categories for participating transplantation teams are baseline: > 3 years before application or no application as of January 1, 2009 (reference category); preparation: 0 to 3 years before application; application: between application and accreditation; and accreditation: from accreditation to January 1, 2009.

†P values refer to the Wald tests comparing a particular category with the reference category (nonrobust).

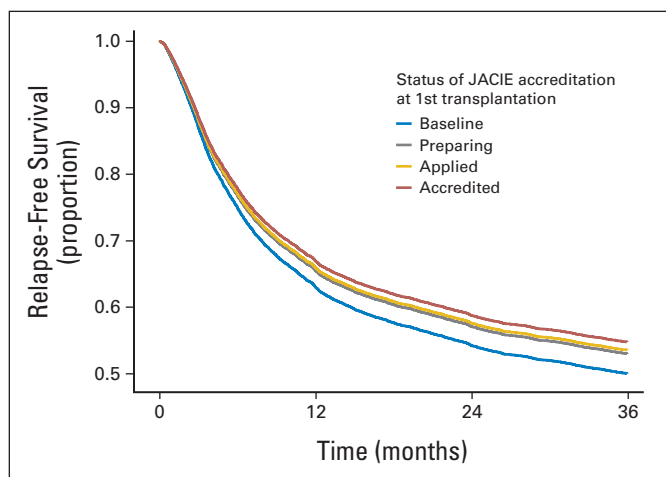


Fig 2. Estimated relapse-free survival probability for patients with chronic leukemia with an intermediate European Group for Blood and Marrow Transplantation risk score of 3 who had a standard allogeneic hematopoietic stem-cell transplantation in 2003. The graph illustrates the systematic improvement with each accreditation step, adjusted for the calendar year and gross national income per capita of the country of the transplantation team. It shows an approximate 4% improvement in relapse-free survival over baseline per accreditation step resulting in an overall improvement of 14% (hazard ratio, 0.86).

for patients who received transplantations in accredited centers compared with patients who received transplantation in centers in the pre-application baseline, preparation, or application periods. This improvement was independent of the year of transplantation, as shown by correcting through stratification for calendar time. The effect of calendar time by itself, when estimated separately, was significant but actually smaller than the effect of JACIE accreditation status. The analysis confirmed the previously shown impact of EBMT risk score for both allogeneic and autologous HSCT and of GNI/capita.^{10,13} The association of outcome with JACIE accreditation status was independent of disease, risk score profile of the patient, conditioning, or GNI/capita of the participating country. The effect was unequivocal and systematic for patients with allogeneic HSCT and clinically relevant with an overall improvement of 11% to 14%. It was of the same order of magnitude between baseline and accreditation status after autologous HSCT but without the same systematic stepwise improvement. The observations were based on survival models of individual patients with identical characteristics (through stratification), respecting the diversity of the patient populations and the teams. They were by definition adjusted for the year of the transplantation, and there were no assumptions of proportionality, except for the JACIE status.

We carefully checked that the covariate or stratification factors did not influence the estimates for accreditation. The adjustment for centers, calendar year, disease, EBMT risk score, donor type, or conditioning should have made patients sufficiently comparable to interpret the effect as “associated with the preparation for and introduction of JACIE accreditation.” This is supported by the fact that the same stepwise improvement was observed when the analysis was restricted to centers involved in the accreditation process. The patient population was admittedly quite heterogeneous. There were several better-known factors influencing outcome after HSCT that were not included in the analysis, such as comorbidity score, viral status, or cytokine polymorphisms.¹⁴⁻¹⁶ This information was not available for everyone in the patient population. There was, however, no suggestion

of an interaction of JACIE accreditation status that could explain accreditation status as a simple surrogate marker for an unknown unrelated effect.

The analysis did not compare centers but merely evaluated the JACIE status of the center at the time of transplantation as an individual risk factor in the prediction of outcome for a patient. This approach was possible because centers in Europe did not embark on the JACIE accreditation process at the same time. Otherwise, center and year of transplantation effect would have been entirely and intrinsically correlated with the JACIE effect. Because centers were starting this process at random points in time, with other centers being in particular phases of accreditation and other patients being treated in those centers at each calendar year, this natural randomization or unpredictable distribution of the center’s JACIE phase over calendar time made it possible to estimate the JACIE effect. Stratifying by calendar time was crucial since calendar time correlated to the within-center evolution of JACIE. For this reason, all models refrained from estimating center effects themselves or from any attempt to separate the JACIE effect from the calendar time effect.

It is therefore likely, even with the limitations of an observational study, that the findings are indeed true observations. The clear stepwise improvement with JACIE accreditation status after allogeneic HSCT, but less so after autologous HSCT, could help further to explain potential effects of JACIE accreditation status. The JACIE quality management system applies to all phases of HSCT,¹⁷⁻²² including patient and donor evaluation, stem-cell collection and processing, clinical care, follow-up, and administration. In autologous HSCT, fewer interactions outside the team take place; nonrelapse mortality is lower, and failure is primarily determined by disease stage and relapse. Less time might be required to achieve improvements, and stepwise changes might be less likely to be documented. In contrast, allogeneic HSCT depends on multiple groups working independently within one team and between donor and recipient teams. Nonrelapse mortality is substantially higher, and more factors need to be controlled to reduce lethal complications. More time might be required to arrive at the benefit of a systematic quality management system through its standard operating procedures.

The results do not imply that the beneficial effect of accreditation will manifest itself in every center. Still, the results support the argument that accreditation should be a goal for all transplantation centers. The value of quality management systems has been documented in laboratory medicine²³⁻³⁰ but has not yet been evaluated in clinical medicine. There are no other quality management systems in clinical medicine comparable to JACIE or its US counterpart FACT, but future studies will yield more information. A minimal case load and a minimum time period of 2 years of transplantation experience are required before application for JACIE accreditation. Hence, any observed effect goes beyond case load or learning. Application for accreditation could reflect the quality of a center or the policy in a given country where JACIE accreditation is mandatory. The difference at baseline between centers becoming accredited over time and centers remaining at baseline and the association of GNI/capita with outcome, independent of JACIE status, could suggest such an element.

Therefore, the improvement in outcome cannot be reduced to center effects, even though they are well described in surgery, in complex medicine, and in HSCT. Such center effects have been attributed to learning curves, experience, and case load, but no uniform pattern has been identified.³¹⁻³⁴ The clear dose-response relationship from

one JACIE category to the next and the inherent comparison of a center with its previous accreditation status gives evidence for a more causal relationship with the accreditation process and could reflect better adherence to evidence in medicine, an accepted quality marker.³⁵ Other explanations are more difficult to consider.

In conclusion, our data indicate that the process of JACIE accreditation, hence the introduction of a clinical quality management system into a transplantation team, can be associated with improved outcome of patients undergoing HSCT. Potential implications of JACIE accreditation for other fields of complex medical treatments need to be considered.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Employment or Leadership Position: Christian Chabannon, JACIE Administrative Office-Barcelona (U) **Consultant or Advisory Role:** Alois

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AUTHOR CONTRIBUTIONS

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