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Hematologic Malignancies

Association of Macroeconomic Factors With Nonrelapse Mortality After Allogeneic Hematopoietic Cell Transplantation for Adults With Acute Lymphoblastic Leukemia: An Analysis From the Acute Leukemia Working Party of the EBMT

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Key Words. Health care expenditure • Human development index • Hematopoietic cell transplantation • Acute lymphoblastic leukemia • Non-relapse mortality

Abstract

Purpose. From a global perspective, the rates of allogeneic hematopoietic cell transplantation (alloHCT) are closely related to the economic status of a country. However, a potential association with outcome has not yet been documented. The goal of this study was to evaluate effects of health care expenditure (HCE), Human Development Index (HDI), team density, and center experience on nonrelapse mortality (NRM) after HLA-matched sibling alloHCT for adults with acute lymphoblastic leukemia (ALL).

Patients and Methods. A total of 983 patients treated with myeloablative alloHCT between 2004 and 2008 in 24 European countries were included.

Results. In a univariate analysis, the probability of day 100 NRM was increased for countries with lower current HCE (8% vs. 3%; $p = .06$), countries with lower HDI (8% vs. 3%; $p = .02$), and centers with less experience (8% vs. 5%; $p = .04$). In addition, the overall NRM was increased for countries with lower current HCE (21% vs. 17%; $p = .09$) and HDI (21% vs. 16%; $p = .03$) and for centers with lower activity (21% vs. 16%; $p = .07$). In a multivariate analysis, the strongest predictive model for day 100 NRM included current HCE greater than the median (hazard ratio [HR], 0.39; $p = .002$). The overall NRM was mostly predicted by HDI greater than the median (HR, 0.65; $p = .01$). Both lower current HCE and HDI were associated with decreased probability of overall survival.

Conclusion. Both macroeconomic factors and the socioeconomic status of a country strongly influence NRM after alloHCT for adults with ALL. Our findings should be considered when clinical studies in the field of alloHCT are interpreted. ***The Oncologist*** 2016;21:377–383

Implications for Practice: Results of allogeneic hematopoietic cell transplantation (alloHCT) and other advanced oncological procedures may vary among countries and be related to various economic factors. This study, which included a homogenous population of patients with acute lymphoblastic leukemia, demonstrated significant associations of health care expenditure and the Human Development Index with nonrelapse mortality and overall survival after transplantation. The findings should be taken into account when clinical studies in the field of alloHCT are interpreted. The study should be followed by further investigation in other fields of oncology.

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Introduction

The outcome of allogeneic hematopoietic cell transplantation (alloHCT) is highly variable and depends on many factors related to features of the disease, patient and donor characteristics, and details of the transplantation procedure. These factors are included in the prognostic scores elaborated by the European Group for Blood and Marrow Transplantation (EBMT) [1]. However, results of alloHCT may also depend on external factors, such as the transplant team and, more widely, the country where the procedure was performed [2, 3]. The significance of external factors is much less well characterized and is rarely considered for interpretation of clinical studies on alloHCT.

From a European and global perspective, the transplant activity in a country is closely related to various economic and socioeconomic indices, such as gross domestic product per capita (GDP), health care expenditure (HCE), and the Human Development Index (HDI) [4]. An association with results has so far been shown only for the latter [5]. Superior leukemia-free survival (LFS) after myeloablative alloHCT for acute myeloid leukemia (AML) was observed in countries with very high HDI values. On the other hand, individual center activity and organization also strongly influence the results of alloHCT [5–8]. In particular, increased nonrelapse mortality (NRM) after alloHCT with reduced-intensity conditioning was observed in centers with very little experience [8]. It can be speculated that economic factors, by affecting the number of transplantations, may also influence the outcome. Furthermore, lower resources may limit the possibility to properly treat patients with severe complications and affect the incidence of NRM. If so, the possibility of modulating such effects by proper organization of the transplant program at national level (i.e., by concentrating it among experienced centers or dispersing it to allow easier patient access) is an important issue.

The aim of this study was to analyze the potential influence of HCE together with team density per population and per area on NRM and general outcome after alloHCT for patients with acute lymphoblastic leukemia (ALL). In addition, we re-evaluated the significance of HDI and center experience, which so far has been studied mainly in a population of AML patients.

Patients and Methods

Study Design and Data Collection

This retrospective multicenter analysis was based on data provided by the registry of the Acute Leukemia Working Party of the EBMT. Centers participating in the EBMT are annually requested to report all consecutive stem cell transplantations and follow-up. The validation and quality control program verifies the computer print-out of the entered data, cross-checks the national registries, and conducts yearly onsite visits of selected teams. Data on HCE as well as data on country areas and populations were obtained from the Eurostat (http://appsso.eurostat.ec.europa.eu) for the year 2008. For calculation of team density per population and per area, the number of transplant teams was counted based on the EBMT membership. HDI values for 2007 were obtained from the 2009 Human Development Report, published by the United Nations [9].

Criteria of Selection

Inclusion criteria were as follows: (a) diagnosis of ALL, (b) first complete remission at the time of alloHCT, (c) age 18–54 years, (d) alloHCT from HLA-identical sibling (i.e., compatible for HLA-A, -B, and -DRB1, as analyzed by using serological or molecular techniques), (e) alloHCT performed between 2004 and 2008 in European centers reporting to the EBMT registry, (f) bone marrow or peripheral blood used as a source of stem cells, (g) myeloablative conditioning (i.e., regimen based on total-body irradiation [TBI] applied at a dose greater than 6 Gy or busulfan administered at a total dose greater than 8 mg/kg).

Patients, Donors, and AlloHCT Procedure

Altogether, 983 patients, including 614 men, treated in 223 transplant centers located in 24 European countries were included in the analysis. The median age was 35 years (range, 18–55 years). Of the 983 patients, 627 had B-lineage ALL. Of 380 patients with reported cytogenetics, 42% were Philadelphia chromosome-positive. TBI was used for conditioning in 820 patients (83%), and peripheral blood was used as a source of stem cells in 656 (67%) cases. Detailed patient and procedure characteristics are listed in Table 1.

Statistical Analysis

The probabilities of early (until day 100) and overall NRM were the primary study endpoints. Relapse incidence (RI), LFS, overall survival (OS), and rates of engraftment and graft-versus-host disease (GVHD) were secondary endpoints. The NRM and RI were calculated by using cumulative incidence curves in a competing risks setting, with death in remission being treated as a competing event to relapse [10, 11]. The LFS was defined as the time interval from alloHCT to relapse or death in remission, while OS was the time from alloHCT to death from any cause. The probabilities of LFS and OS were calculated by using the Kaplan-Meier estimate.

HCE (current, public, private, and as percentage of GDP), team density (i.e., the number of transplant centers per country population and area), HDI, and center experience (number of alloHCT meeting selection criteria for this study, performed during study period) were independent variables. For the purpose of the analyses, they were categorized by medians. The comparisons were done with the use of the Gray test for NRM and RI and log-rank test for LFS and OS.

For each socioeconomic factor (current, public, private HCE; HCE as percentage of GDP; HDI) as well as for team density per population, team density per area, and center experience, a separate Cox proportional hazard model was created, adjusted for other potential risk factors of NRM (age, interval from diagnosis to alloHCT, source of stem cells, type of conditioning, and female donor to male recipient combination). The socioeconomic factors, team density, and center experience could not be combined in the same model because of strong cross-correlations. The models were created for both day 100 NRM and overall NRM. Factors affecting RI, LFS, and OS were not evaluated in multivariate analyses.

Table 1. Patients, donors, transplantation procedure, economic, and socioeconomic indices

Patient and procedure characteristics	Value
Patients (*n*)	983
Median patient age (range), yr	35 (18–55)
Median year of transplantation (range)	2006 (2004–2008)
Median interval from diagnosis to transplantation (range), days	158 (42–231)
Recipient sex	
Female	365 (37)
Male	614 (63)
Unknown	4
Philadelphia chromosome	
Negative	222 (58)
Positive	158 (42)
Unknown	603
Immunologic subtype of ALL	
B cell	627 (75)
T cell	206 (25)
Other/unknown	150
Type of conditioning	
TBI-based	820 (83)
Chemotherapy-based	163 (17)
Source of stem cells	
Bone marrow	327 (33)
Peripheral blood	656 (67)
Economic and socioeconomic indices	
Median current HCE (range), €	3,222 (840–5,207)
Median HCE (% of GDP)	9 (5.4–11.2)
Median private HCE (range), €	892 (177–1,968)
Median public HCE (range), €	2,662 (618–4,091)
Median teams per 1 million inhabitants (*n*)	0.441 (0.156–3.279)
Median teams per 10,000 km^2 (*n*)	0.535 (0.059–3.279)
Median HDI	0.863 (0.679–0.938)
Median alloHCTs[a] between 2004 and 2008 (*n*)	6 (1–25)

Unless otherwise noted, values are *n* (%).
[a]Transplantation procedures according to selection criteria chosen for this study.
Abbreviations: ALL, acute lymphoblastic leukemia; alloHCT, allogeneic hematopoietic cell transplantation; HCE, health care expenditure; HDI, Human Development Index; TBI, total-body irradiation.

All *p* values are two-sided, with a type 1 error rate fixed at .05. All statistical tests were performed with R software, version 3.1.0 (R Core Team, Vienna, Austria, https://www.r-project.org).

Results

Early Nonrelapse Mortality

The median duration of follow-up for survivors was 34 months (range, 1–86 months). In univariate analysis, early (up to day +100) NRM was increased for centers located in countries with HDI at the median or less (mean ± SE: 8% ± 1% vs. 3% ± 1%; $p = .02$) and for centers with lower transplant activity (8% ± 1% vs. 5% ± 1%; $p = .04$). There was also a tendency for increased early NRM for countries with the current HCE at or less than the median (8% ± 1% vs. 3% ± 1%; $p = .06$) (Table 1, Fig. 1). In multivariate analysis, the strongest effect was observed when current HCE was included in the model (hazard ratio [HR], 0.39; 95% confidence interval [CI], 0.21–0.71; $p = .002$). Significant associations were also observed for models that included public HCE, private HCE, and HCE as percentage of GDP (Table 2). No significant associations were found between early NRM and team density.

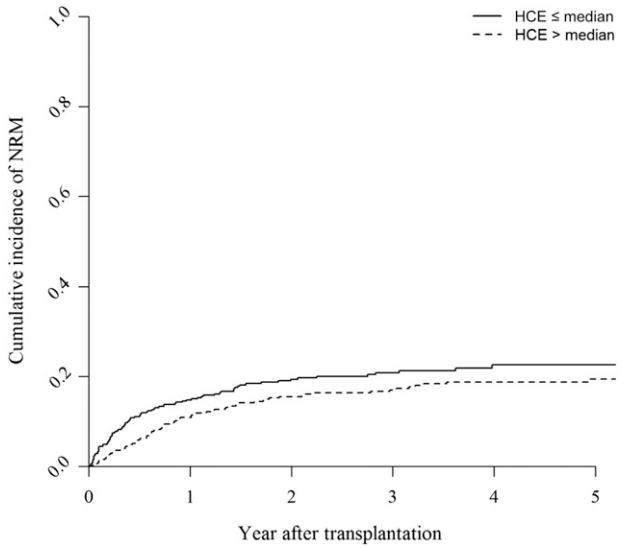

Figure 1. Nonrelapse mortality according to current health care expenditure.
Abbreviations: HCE, health care expenditure; NRM, nonrelapse mortality.

Higher current HCE and HDI were associated with higher incidence of engraftment (99% ± 1% vs. 98% ± 1% at day 45 for both indices; $p < .01$). No significant associations were found with respect to grade 2–4 or grade 3–4 acute GVHD or chronic GVHD.

Overall Nonrelapse Mortality

The cumulative incidence of NRM at 3 years was increased for countries with HDI at the less than the median (21% ± 2% vs. 16% ± 2%; $p = .03$) (Fig. 2). A trend toward higher overall NRM was observed for less experienced centers (21% ± 2% vs. 16% ± 2%; $p = .07$) and those located in countries with current HCE at or less than the median (21% ± 2% vs. 17% ± 2%; $p = .09$) (Table 2). Among multivariate models, the strongest predictive value was found for HDI (HR, 0.65; 95% CI, 0.47–0.91; $p = .01$). A significant effect was also observed for current HCE (Table 3). Once again, team density did not influence the risk for overall NRM. Reasons for NRM did not differ significantly for alloHCT performed in countries with higher (greater than the median) compared with lower (at or less than the median) current HCE, as well as according to HDI (supplemental online Table 1).

Relapse Incidence and Survival

The economic and socioeconomic factors had no significant influence on the RI. There was a trend toward increased RI at 3

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Table 2. Results of univariate analysis of associations of economic and socioeconomic factors with outcome

Variable	Patients (*n*)	NRM (100 days)	NRM (3 yr)	RI (3 yr)	LFS (3 yr)
HCE current					
At or less than median	521	8 ± 1	21 ± 2	31 ± 2	48 ± 3
Greater than median	462	3 ± 1	17 ± 9	25 ± 2	58 ± 2
p value		.06	.09	.19	.01
HCE as percentage of GDP					
At or less than median	540	7 ± 1	20 ± 2	29 ± 2	51 ± 2
Greater than median	443	4 ± 1	18 ± 2	26 ± 2	56 ± 3
p value		.39	.4	.44	.16
HCE private					
At or less than median	562	7 ± 1	19 ± 2	29 ± 2	51 ± 2
Greater than median	421	4 ± 1	18 ± 2	26 ± 2	55 ± 2
p value		.55	.57	.55	.3
HCE public					
At or less than median	534	8 ± 1	20 ± 2	31 ± 2	49 ± 2
Greater than median	449	4 ± 1	18 ± 2	25 ± 2	57 ± 2
p value		.16	.22	.18	.03
HDI					
At or less than median	542	7 ± 1	21 ± 2	30 ± 2	49 ± 2
Greater than median	470	3 ± 1	16 ± 2	25 ± 2	58 ± 2
p value		.02	.03	.32	.008
Team density per population					
At or less than median	580	6 ± 1	19 ± 2	25 ± 2	55 ± 2
Greater than median	403	5 ± 1	18 ± 2	31 ± 2	51 ± 3
p value		.73	.81	.08	.1
Team density per area					
At or less than median	513	6 ± 1	19 ± 2	28 ± 2	52 ± 2
Greater than median	470	6 ± 1	19 ± 2	27 ± 2	54 ± 2
p value		.8	.9	.49	.55
Team density per area					
At or less than median	509	8 ± 1	21 ± 2	28 ± 2	50 ± 2
Greater than median	474	5 ± 1	16 ± 2	27 ± 2	56 ± 3
p value		.04	.07	.5	.04

Unless otherwise noted, values are expressed as % (mean ± SD).
Abbreviations: GDP, gross domestic product per capita; HCE, health care expenditure; HDI, Human Development Index; LFS, leukemia-free survival; NRM, nonrelapse mortality; RI, relapse incidence.

years for centers located in countries with team density per population greater than the median (31% ± 2% vs. 25% ± 2%; $p = .08$) (Table 2).

The probability of LFS at 3 years was decreased for centers from countries with an HDI at or less than the median (49% ± 2% vs. 52% ± 2%; $p = .008$) (Fig. 3), current HCE at or less than the median (48% ± 2% vs. 58% ± 2%; $p = .01$) (Fig. 4), public HCE at or less than the median (49% ± 2% vs. 57% ± 2%; $p = .03$), and less activity (50% ± 2% vs. 56% ± 4%; $p = .04$) (Table 2). The probability of OS at 3 years was lower for centers located in countries with HDI at or less than the median (57% ± 2% vs. 65% ± 2%; $p = .004$) and current HCE at or less than the median (57% ± 2% vs. 65% ± 2%; $p = .006$).

Discussion

AlloHCT is known to be one of the most expensive medical procedures. Early costs are related to verification of donor compatibility, procurement of hematopoietic stem cells, and initial hospital stay. The latter includes costs of conditioning therapy, diagnostics, prevention and treatment of acute complications, and maintaining the appropriate setting (i.e., rooms with laminar air flow, positive pressure, and antibacterial filters). Late costs include monitoring of the engraftment, disease status, and late complications, as well as appropriate interventions [12]. The overall expenses may vary according to the donor type (higher for unrelated donors than for sibling donors) [12–14], the source of stem cells (higher for cord blood than for bone marrow or peripheral blood) [14], and intensity of the conditioning regimen [14, 15]. The costs may also depend on the patient selection, being increased for individuals with high risk for treatment failure [16]. Marked differences between costs of alloHCT from sibling donors have been reported between countries (e.g., $148,709 [initial hospitalization] in the U.S. compared with $17,914 in India)

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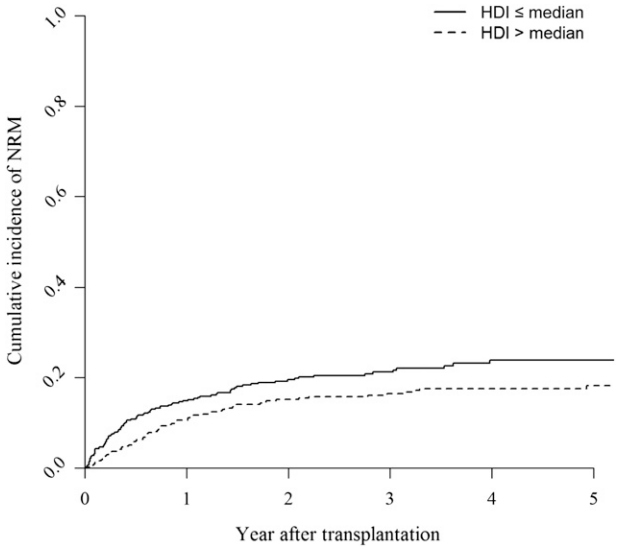

Figure 2. Nonrelapse mortality according to the Human Development Index.

Abbreviations: HDI, health care expenditure; NRM, nonrelapse mortality.

[17, 18]. These data may reflect lower personnel and infrastructural costs in less developed countries but also limited access to some expensive components of the procedure, including drugs and laboratory diagnostics.

In view of the above considerations, it may be expected that availability of alloHCT may differ among countries and may be related to their general economic status. Indeed, a strong correlation between alloHCT rate and all, GDP per capita, HCE, and HDI has been previously demonstrated [1, 2]. An association of HCE with the results of alloHCT, however, has not so far been studied. On the one hand, it may be hypothesized that limited access to the most expensive pharmaceuticals and diagnostic procedures may contribute to increased morbidity and mortality. On the other hand, focusing limited resources on the most cost-effective procedures or appropriate organization of the transplantation-related health care system may potentially overcome the negative effect of restricted resources. In the current study, we attempted to evaluate the effect of all, purely economic, socioeconomic, and organizational aspects, together with individual center experience, on the results of sibling alloHCT. A relatively homogenous population of ALL patients treated in first complete remission with transplantations preceded by myeloablative conditioning was chosen. Transplantations were performed in a relatively recent period with sufficient follow-up. We focused on NRM as a primary endpoint because it potentially is the most susceptible to the influence of economic factors. Each variable was analyzed separately because most of them strongly correlated with each other. The goal was to select the most powerful associations with outcome.

The results of our study clearly demonstrate an association of both HCE and HDI with early and overall NRM. It appears that the current HCE is the strongest predictor of early NRM compared with private or public HCE, indicating that the source of reimbursement is less important than the overall input. These results may confirm the hypothesis that limited HCE is associated with restricted access to some particularly expensive forms of supportive therapy. Because acute GVHD and infections are the most frequent reasons of NRM after alloHCT, the differences could be due to the selection or availability of immunosuppressive and anti-infectious agents. Unfortunately, because of the retrospective nature of the study, detailed analysis of the reasons of NRM was not possible. In a univariate analysis, early NRM was increased for centers with lower than median transplant rates, which could suggest that the team experience may compensate for the negative effect of lower HCE. However, results of a multivariate analysis did not confirm the independent effect of the center experience.

The issue of late NRM is more complex. Although in the early post-transplant period patients tend to remain in or close to the hospital, in the later phase they usually stay at home. Therefore, early recognition of life-threatening complications and their treatment depends on the ability of the patient to attend the follow-up visits. The incidence of severe late infections may, in turn, be affected by the local social conditions. As demonstrated by Khera et al. in the Mayo Clinic population of alloHCT recipients, the procedure itself is associated with high financial burden [19]. Forty-seven percent of patients declared reduction of their income by greater than 50% due to loss of employment, insurance, out-of-pocket expenses, and deterioration of their health and functional status. It may be easily speculated that in countries with lower GDP per capita such effects may be even more strongly expressed and that deterioration of the living conditions may influence the risk for NRM. Indeed, although both current HCE and HDI influenced the overall NRM in the present study, the effect of HDI was stronger. This suggests that, for later events, the general socioeconomic status of a country and its citizens may be particularly important. The values of HDI depend on the GDP per capita but also on education and life expectancy. The latter two components may be related to the general lifestyle, once again potentially associated with late complications and NRM. Finally, it may be speculated that in countries with low HDI the use of alloHCT is partially restricted to patients with high education and financial status. This could cause a selection bias, flattening potential differences between outcomes of alloHCT in countries with different HDI. Unfortunately, the retrospective nature of this study did not allow for evaluation of individual patients' socioeconomic status.

Interpretation of the data regarding LFS and OS is even more difficult because these endpoints depend not only on NRM but also on RI. The incidence of relapse, in turn, may be associated with disease status before alloHCT and, in particular, with the level of minimal residual disease, which reflects the efficacy of the preceding conventional-dose chemotherapy [20]. It may also be influenced by the use of tyrosine kinase inhibitors in case of Philadelphia chromosome-positive ALL. In the current study, the economic and socioeconomic factors were not associated with RI, while both current HCE and HDI strongly influenced the probabilities of LFS and OS. This suggests that the effect on survival was predominantly dependent on NRM.

It may be hypothesized that a proper organization of the transplantation-related health care system may limit the negative effect of limited resources. Identification of the optimal number of transplant teams to allow easy access while enabling sufficient center experience seems to be one of the most

Table 3. Results of multivariate analysis of associations of economic and socioeconomic factors with early and overall nonrelapse mortality

	NRM at day +100		Overall NRM	
Factor	**HR (95% CI)**	***p* value**	**HR (95% CI)**	***p* value**
HCE current	0.39 (0.21–0.71)	.002	0.72 (0.52–0.99)	.04
HCE as percentage of GDP	0.49 (0.27–0.87)	.02	0.87 (0.64–1.18)	.36
HCE private	0.53 (0.3–0.96)	.04	0.91 (0.66–1.24)	.55
HCE public	0.42 (0.23–0.76)	.005	0.79 (0.58–1.09)	.15
Team density per population	0.76 (0.43–1.33)	.34	0.96 (0.7–1.32)	.81
Team density per area	1.11 (0.64–1.91)	.72	0.92 (0.67–1.27)	.62
HDI	0.42 (0.23–0.77)	.005	0.65 (0.47–0.91)	.01
No. of alloHCT[a]	0.72 (0.41–1.24)	.24	0.75 (0.55–1.03)	.07

All variables were categorized by medians. Each factor was individually added to a Cox proportional hazard model that included other potential risk factors of nonrelapse mortality (age, interval from diagnosis to allogeneic hematopoietic cell transplantation, source of stem cells, type of conditioning, and female donor to male recipient combination). Only results related to socioeconomic indices, team density, and center experience are presented.
[a]Transplantation procedures performed between 2004 and 2008 according to the selection criteria chosen for this study.
Abbreviations: alloHCT, allogeneic hematopoietic cell transplantation; CI, confidence interval; GDP, gross domestic product per capita; HCE, health care expenditure; HDI, Human Development Index; HR, hazard ratio; NRM, nonrelapse mortality.

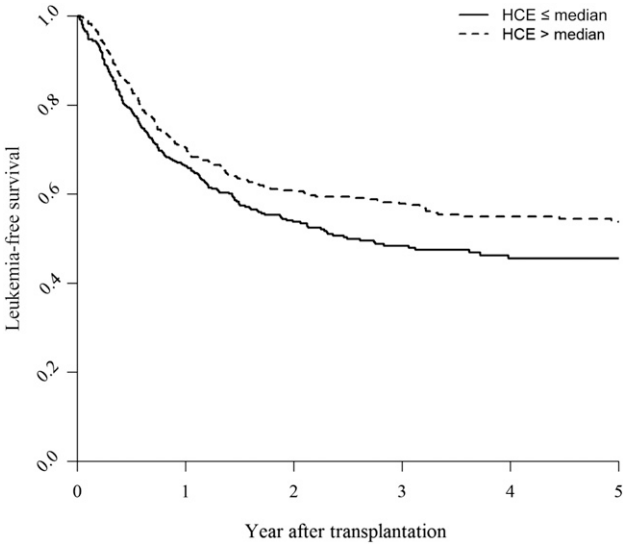

Figure 3. Leukemia-free survival according to current health care expenditure.
Abbreviations: HCE, health care expenditure; NRM, nonrelapse mortality.

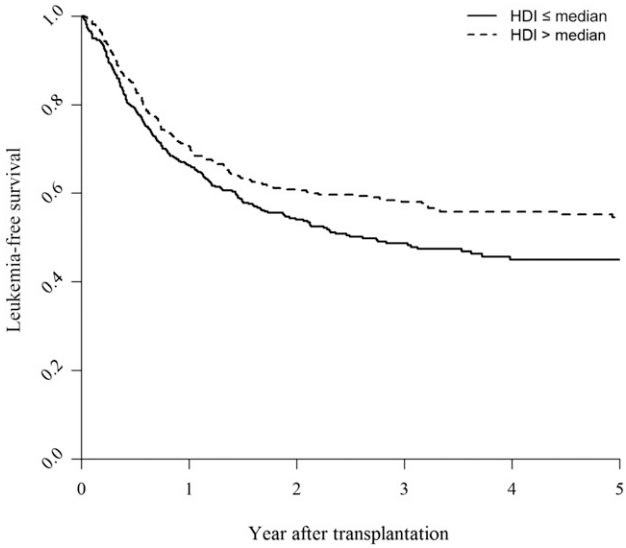

Figure 4. Leukemia-free survival according to the Human Development Index.
Abbreviations: HDI, health care expenditure; NRM, nonrelapse mortality.

important issues. The results of the current study do not allow us to address this question. Neither team density per population nor per country area was associated with outcome. It probably reflects high diversity among the European countries, some of them being very densely populated and others, not. Therefore, it seems that no universal pattern can be determined. As suggested by Gratwohl and colleagues' study, the results of alloHCT may be improved by the introduction of a quality control system (e.g., JACIE [Joint Accreditation Committee International Society for Cellular Therapy and the European Group for Blood and Marrow Transplantation]) [21].

Conclusion

The results of the current study indicate that both macroeconomic factors and the socioeconomic status of a country, as reflected by HCE and HDI, strongly influence the early and overall NRM, as well as OS, after alloHCT for adults with ALL. Our findings highlight the role of nonmedical prognostic factors associated with transplantation outcome and should be considered when clinical studies on alloHCT are interpreted. Further investigation on associations of economic factors with treatment results is warranted in other fields of oncology.

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