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A B S T R A C T

For patients with acute lymphoblastic leukemia (ALL), allogeneic hematopoietic cell transplantation (alloHCT) offers a potential cure. Life-threatening complications can arise from alloHCT that require the application of sophisticated health care delivery. The impact of country-level economic conditions on post-transplantation outcomes is not known. Our objective was to assess whether these variables were associated with outcomes for patients transplanted for ALL. Using data from the Center for Blood and Marrow Transplant Research, we included 11,261 patients who received a first alloHCT for ALL from 303 centers across 38 countries between the years of 2005 and 2013. Cox regression models were constructed using the following macroeconomic indicators as main effects: Gross national income per capita, health expenditure per capita, and Human Development Index (HDI). The outcome was overall survival at 100 days following transplantation. In each model, transplants performed within lower resourced environments were associated with inferior overall survival. In the model with the HDI as the main effect, transplants performed in the lowest HDI quartile (n = 697) were associated with increased hazard for mortality (hazard ratio, 2.42; 95% confidence interval, 1.64 to 3.57; $P < .001$) in comparison with transplants performed in the countries with the highest HDI quartile. This translated into an 11% survival difference at 100 days (77% for lowest HDI quartile versus 88% for all other quartiles). Country-level macroeconomic indices were associated with lower survival at 100 days after alloHCT for ALL. The reasons for this disparity require further investigation.

INTRODUCTION

The application of allogeneic hematopoietic cell transplantation (alloHCT) in the treatment of patients with hematological malignancies continues to increase in the United States and worldwide, with more than 8000 allogeneic transplants performed in the United States in 2015 [1] and more than 34,000 globally in 2012 [2]. Though transplant and supportive care techniques have improved [3], the success of transplant is limited by persistently high rates of treatment-related morbidity and mortality [4]. Across centers and physicians, there is documented variation in transplant practices that may impact outcomes [5-9]. Indeed, center-specific outcomes reporting in the United States demonstrates 1-year survival differences among transplant centers, even when accounting for relevant disease and patient characteristics [10].

Acute lymphoblastic leukemia (ALL) is a life-threatening disease that affects children and adults. Historically, HCT has provided an opportunity for cure in this disease in defined subsets of individuals, a conclusion that is supported by randomized trials and consensus statements [11,12]. Overall transplant rates in patients with ALL remain relatively low, with a recent California registry analysis showing that approximately 14% of individuals with ALL who were over the age of 15 years received alloHCT [13]. Additionally, ALL represents a disease in which substantial practice variation exists in the application of standard transplant techniques, in which patients come to transplantation after already experiencing significant primary treatment intensity, and in which the complications of the procedure can be quite high. Thus, ALL represented an ideal condition to investigate variation in postprocedural mortality across treatment settings.

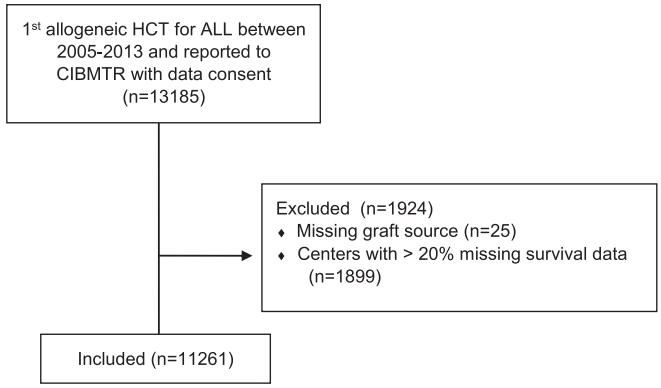
Because economic inputs may contribute to transplant practice variation and outcomes [14-16], we hypothesized that transplant survival differences would exist internationally on the basis of country-level macroeconomic indicators. We tested this hypothesis by investigating allogeneic transplant outcomes internationally for ALL. We chose 100-day post-translant survival as an outcome that was likely to be sensitive to the practices of the treating transplant center.

METHODS

Data Sources

The Center for Blood and Marrow Transplant Research (CIBMTR) is a prospectively maintained transplant database that captures transplant data from more than 500 transplant centers worldwide. Data are submitted to a statistical center at the Medical College of Wisconsin in Milwaukee. Participating

A. CONSORT Diagram for cohort construction



B. Population summary by macroeconomic indicator

Gross National Income per Capita

Category	Number of Transplants
High Income	10493
Upper Middle Income	607
Lower Middle Income / Low Income	155

Health Expenditure Per Capita (USD)

Category	Number of Transplants
Quartile 4 (>$5904)	8714
Quartile 3 ($2508-$5093)	864
Quartile 2 ($797-$2507)	1413
Quartile s (<$797)	249

Human Development Index

Category	Number of Transplants
Quartile 4 (>0.913)	8937
Quartile 3 (0.8806-0.912)	1092
Quartile 2 (0.780-0.8805)	528
Quartile 1 (<0.780)	698

Figure 1. Cohort description.

centers are required to report all transplantations consecutively; patients are followed longitudinally, and compliance is monitored by onsite audits. Computerized checks for discrepancies, physicians' review of submitted data, and onsite audits of participating centers ensure data quality. Observational studies conducted by the CIBMTR are performed in compliance with all applicable federal regulations pertaining to the protection of human research participants. Protected Health Information used in the performance of such research is collected and maintained in the CIBMTR's capacity as a Public Health Authority under the HIPAA Privacy Rule.

Patients

This study included 11,261 patients who received a first alloHCT for ALL from 303 centers across 38 countries between the years of 2005 and 2013 (Figure 1A). This population represents roughly 25% of all global alloHCT activity for ALL during this time period [2]. All ages, graft sources, donor types, conditioning regimens (total body irradiation based versus not), conditioning regimen intensities, and disease subtypes (Philadelphia chromosome negative, Philadelphia chromosome positive, and T cell ALL) were included. The population was restricted to centers contributing > 80% rates of overall data completeness to the CIBMTR. For included centers, data completeness was > 90% at the time point of 100 days after cell infusion (day 100), the primary survival endpoint in this analysis. Because data completeness rates were lower at all subsequent time points after 100 days, we were not able to include long term disease free or overall survival as endpoints in this analysis.

Macroeconomic Indicators

To facilitate the investigation of the relationship between economic indicators and transplant outcomes, the following macroeconomic indicators were ascertained on a country-level basis using publicly available datasets, with each contributing transplant center assigned the respective indicators associated with its home country: Human Development Index (HDI) (http://hdr.undp.org/en/content/human-development-index-hdi), a composite variable containing information about life expectancy, education, and gross national income (GNI); health expenditure per capita (HEPC) (http://data.worldbank.org/indicator/SH.XPD.PCAP), GNI per capita (http://data.worldbank.org/indicator/NY.GNP.PCAP.PP.CD), and GNI per capita grouping into high-income countries (HICs), high middle-income countries (HMICs), low middle-income countries (LMICs), and low-income countries (LICs) (http://data.worldbank.org/country). Because centers contributed data from 2005 to 2013, average macroeconomic indicator values for each country during this time period were computed. Summary population data for the macroeconomic variables are included in Figure 1B. For a complete list of included countries and contributing centers per country, please see the Appendix (Supplementary Table S1).

Statistical Analysis

The main outcome of this study was overall survival at 100 days after transplantation, defined as time to death from any cause. Patient-, disease-, and transplant related variables were summarized using descriptive statistics for the entire population taken together and also separated by GNI per capita grouping (HIC/HMIC/LMIC/LIC). The effects of country-level macroeconomic indicators on 100-day overall survival were analyzed using Cox proportional hazards regression models. Separate multivariable models were constructed for GNI per capita, HEPC, and the HDI. For each model, the following variables were included: macroeconomic indicator (main effect), age, ALL subtype, disease status, time from diagnosis to transplant, conditioning regimen intensity, donor and graft type, year of transplant, and Karnofsky performance status. Marginal Cox models were used to account for clustering within each country. The proportional hazards assumption was tested for each factor using a time-dependent covariate approach. Backward elimination procedures were used to identify significant variables to include in the final model (significance level $P < .05$). Potential interactions between the main effect and all significant covariates were examined.

RESULTS

Worldwide Use of alloHCT for ALL

11,261 patients underwent a first alloHCT for ALL at 1 of 303 centers in 38 countries between the years of 2005 and 2013. Descriptive statistics for the overall population are provided in Table 1. The median age of the population was 26 years (range, <1 to 75 years). A preponderance of patients were men (59%), with most having a high performance status (85%) and most transplanted in first complete remission (CR1) (54%) with a substantial minority transplanted in second complete remission (CR2) (29%), and 17% in neither CR1 or CR2. Myeloablative total body irradiation–based conditioning was used most frequently, and peripheral blood from HLA-identical sibling donors or unrelated donors were the most common graft and donor type combinations. Haploidentical transplants were included and are contained within the "other related" categories in Table 1. Descriptive statistics for disease, patient and transplant variables by GNI category are provided in the Appendix (Supplemental Table S2).

Table 1
Characteristics of Patients Undergoing alloHCT for ALL between 2005 and 2013

Variable	Report
Patients	11,261
Centers	303
Countries	38
Age	
≤18 yr	3762 (33)
>18 yr	7499 (67)
Sex	
Male	6690 (59)
Female	4567 (41)
Karnofsky performance status	
80–100%	9545 (85)
<80%	787 (7)
Time from diagnosis to transplant (CR1)	
0–6 mos	3615 (60)
6+ mos	2428 (40)
ALL subtype	
ALL—B cell lineage, Ph+	1680 (15)
ALL—B cell lineage, Ph–	7887 (70)
ALL—T cell lineage	1677 (15)
Disease status at transplant	
CR1	6072 (54)
CR2	3265 (29)
Other	1924 (17)
Year of HCT	
2005–2008	4607 (41)
2009–2013	6654 (59)
Conditioning regimen	
TBI containing	8859 (79)
Chemotherapy only	2374 (21)
Conditioning regimen intensity	
Nonmyeloablative	1330 (12)
Myeloablative	9794 (87)
Donor/graft type	
HLA-identical sibling/BM	1487 (13)
HLA-identical sibling/PB	2829 (25)
Twin	33 (<1)
Other related/BM	253 (2)
Other related/PB	376 (3)
URD/BM	1566 (14)
URD/PB	3003 (27)
Cord blood	1650 (15)
Missing	64 (<1)
Median follow-up of survivors, months	50 (<1–127)

Data are presented as n, n (%), or median (range).
Ph+ indicates Philadelphia chromosome positive; Ph-, Philadelphia chromosome negative; TBI, total body irradiation; HLABM, bone marrow; PB, peripheral blood; URD, unrelated donor.

Effect of Macroeconomic Indices upon 100-Day Overall Survival

Multivariable models for each country-level macroeconomic indicator as the main effect are presented in Table 2. With transplants performed in high income countries as the reference, GNI per capita was associated with 100-day survival, and transplants performed in HMICs, LMICs, and LICs had higher hazards for death (HMICs: hazard ratio [HR], 2.12 [95% confidence interval (CI), 1.51 to 2.97], $P < .0001$; LMICs/LICs: HR, 1.77 [95% CI, 1.28 to 2.46], $P = .00061$). Though disease subtype, disease status, Karnofsky performance status, conditioning intensity, and year of transplant were also statistically significant in multivariable analysis, the only variable with hazard ratios of the same or higher magnitude as GNI per capita was disease status, and specifically transplants performed in CR2 (HR, 2.09 [95% CI, 1.81 to 2.40], $P < .0001$) or beyond relative to early CR1. Complete multivariable models with all hazard ratios, confidence intervals and P values for significant covariates are included in the Appendix (Supplemental Table S3).

Similar findings were observed for other country level macroeconomic indicators. For HEPC, transplants performed in countries with HEPC <US$797 were associated with worse overall survival at 100 days than transplants performed in countries with HEPC >US$5094 (HR, 1.56 [95% CI, 1.11 to 2.18] $P = .0098$). For HDI, transplants performed in countries with HDI <.780 were associated with worse 100-day overall survival than transplants performed in countries with HDI >.913 (HR, 2.19 [95% CI, 1.66 to 2.87], $P < .0001$).

To illustrate the magnitude of 100-day overall survival differences by country level macroeconomic indices, Kaplan-Meier survival curves for transplants performed in the highest HDI quartile versus all other transplants are shown in Figure 2, demonstrating an adjusted 100-day overall survival of 88% (95% CI, 87% to 89%) for the highest HDI quartile versus 78% (95% CI, 74% to 81%) for the lowest HDI quartile.

In a sensitivity analysis, models were constructed in which transplants performed in the United States were not included, as the United States represented a large number of transplants performed within a high-income setting. In this analysis, the findings remained unchanged (data not shown).

Table 2
Multivariable Models for Effects of Country-Level Macroeconomic Indicators on 100-Day Overall Survival Following alloHCT for ALL

Main Effect: GNI per Capita				
Category	n	HR	95% CI	*P* Value
HIC	10,493	1.00		<.0001
UMIC	607	2.12	1.51–2.97	<.0001
LMIC/LIC[c]	155	1.77	1.28–2.46	.0006
Main effect: HEPC (USD)				
Quartile 4 (>$5094)	8714	1.00		.0150
Quartile 3 ($2508–$5093)	864	1.25	.97–1.62	.0872
Quartile 2 ($797–$2507)	1413	1.45	.82–2.55	.2032
Quartile 1 (<$797)	249	1.56	1.11–2.18	.0098
Main effect: HDI				
Quartile 4 (>.913)	8937	1.00		<.0001
Quartile 3 (.8806–0.912)	1092	1.10	.85–1.41	.48
Quartile 2 (.780–.8805)	528	1.02	.56–1.84	.95
Quartile 1 (<.780)	698	2.19	1.66–2.87	<.0001

In all multivariable models, other statistically significant associations were seen for the following variables: age, ALL subtype, time from diagnosis to HCT, Karnofsky performance status, conditioning regimen intensity, and year of treatment.

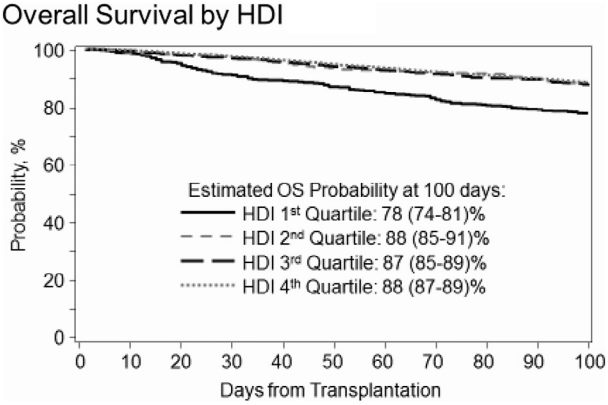


Figure 2. Kaplan-Meier curve for 100-day overall survival after alloHCT, by country-level HDI quartile grouping.

Multivariable Models Including Interaction Terms for Disease-, Patient-, and Transplant-Related Variables

Table 3 shows a multivariable model for 100-day overall survival in which the main effect is the HDI with interaction terms introduced for the other variables. In general, transplants performed in LICs were associated with worse survival in nearly all categories examined. Though some categories were associated with particularly worse survival in LICs (eg, other related bone marrow graft source transplants, which include haploidentical transplants [HR, 6.86 (95% CI, 5.53 to 8.51), $P < .0001$]), conclusions are limited by small sample sizes within individual categories, requiring further validation of these findings.

Table 3
Multivariable Model for 100-Day Survival with HDI as Main Effect and Interaction Terms Introduced for Each Covariate (HRs Compare Lowest HDI Quartile with 3 Highest Quartiles)

Group	HR	Lower CL	Upper CL	*P* Value
ALL subtype				
B cell, Ph+	2.51	1.37	4.60	.0028
B cell, Ph-	2.32	1.81	2.96	<.0001
T cell	3.69	3.03	4.50	<.0001
Donor/graft				
HLA-identical sibling/BM	3.29	2.74	3.94	<.0001
HLA-identical sibling/PB	2.09	1.29	3.37	.0026
Twins	3.97	.65	24.38	.1360
Other related/BM	6.86	5.53	8.51	<.0001
Other related/PB	1.58	.58	4.33	.3696
URD/BM	3.05	2.49	3.73	<.0001
URD/PB	2.43	1.74	3.38	<.0001
Cord blood	2.40	2.06	2.81	<.0001
Disease status				
CR1, 0–6 mo	2.84	1.51	5.35	.0012
CR1, 6+ mo	3.19	2.34	4.35	<.0001
CR2	2.55	2.16	3.01	<.0001
CR3	1.84	1.41	2.39	<.0001
Relapse	2.16	1.47	3.19	<.0001
PIF	2.78	1.59	4.86	.0003
Karnofsky performance status				
80–100%	2.58	2.07	3.21	<.0001
<80%	2.15	1.37	3.39	.0009
Conditioning Intensity				
Nonmyeloablative	1.41	.48	4.09	.5324
Myeloablative	2.75	2.28	3.31	<.0001
Year				
2005–2008	2.43	1.72	3.44	<.0001
2009–2013	2.65	2.16	3.24	<.0001

CL indicates confidence limit; CR3, third complete remission; PIF, primary induction failure.

Causes of Death

Because of the observed 100-day survival differences by economic indicators, we tabulated reported cause of death data as reported to the CIBMTR for centers included in this analysis. Figure 3 shows charts depicting reported causes of death within 100 days by transplants performed in HICs versus HMICs/LMICs/LICs. The most frequent causes of death reported were primary disease, graft-versus-host disease, infection, and organ toxicity. Formal comparisons between economic settings were not possible, though it is notable that infections (39%) represented a high proportion of deaths in HMIC/LMIC/LIC settings.

DISCUSSION

We found that country-level macroeconomic indices were associated with 100-day survival after alloHCT for ALL. This effect was seen in multivariable analysis after adjusting for known relevant disease-related, patient-related and transplant-related factors shown to be associated with survival in other studies. This effect was also seen across different, albeit correlated, economic indicators. The stratification of the population and the presence or absence of a stepwise effect across variables differed by particular macroeconomic indicator, but the overall effect was similar. Most care delivery through 100 days post-alloHCT includes a high degree of transplant center involvement, suggesting a contribution of transplant center care to the observed survival differences across economic settings.

Our findings are consistent with survival differences seen in pediatric ALL care in the nontransplant setting. Prior studies in this population have shown higher treatment-related mortality and lower overall survival in lower-resourced countries [17-19]. In higher resourced environments, allogeneic transplant analyses that include all diseases have shown center-level variation in outcomes, and the Stem Cell Therapeutic Outcomes Database provides a center-level comparison for 1-year overall survival that illustrates these differences. Though the Stem Cell Therapeutic Outcomes Database analysis demonstrates a center effect on survival, these data have not been linked to underlying economic conditions within these higher resourced settings. Internationally, economic indicators have been associated with rates of transplantation and other transplant process measures [20,21]. Previous studies of the relationships of macroeconomic indicators and transplantation have been performed with less geographic scope or with longer term endpoints that may reflect other nontransplant components to leukemia care delivery. Nonetheless, these studies have also demonstrated similar relationships (ie, that transplants performed in higher resourced settings are associated with improved outcomes) [22,23]. To our knowledge, ours is the first study that has been performed worldwide that shows the effect of economic indicators on short term outcomes following transplantation, which are plausibly linked to factors related to transplant center practice. Ours is also the first international study in transplant for ALL, a disease with high pediatric and adult representation, and is strengthened by our inclusion of a large dataset across countries of varying economic backgrounds.

The mechanism for the link between country-level macroeconomic indicators and post-transplant outcomes is unclear. One possibility is that transplants performed in lower economic settings are associated with decreased availability of resources that affect HCT and early post-HCT care delivery. Prior work has documented extensive variability in provision of transplant supportive practices within the United

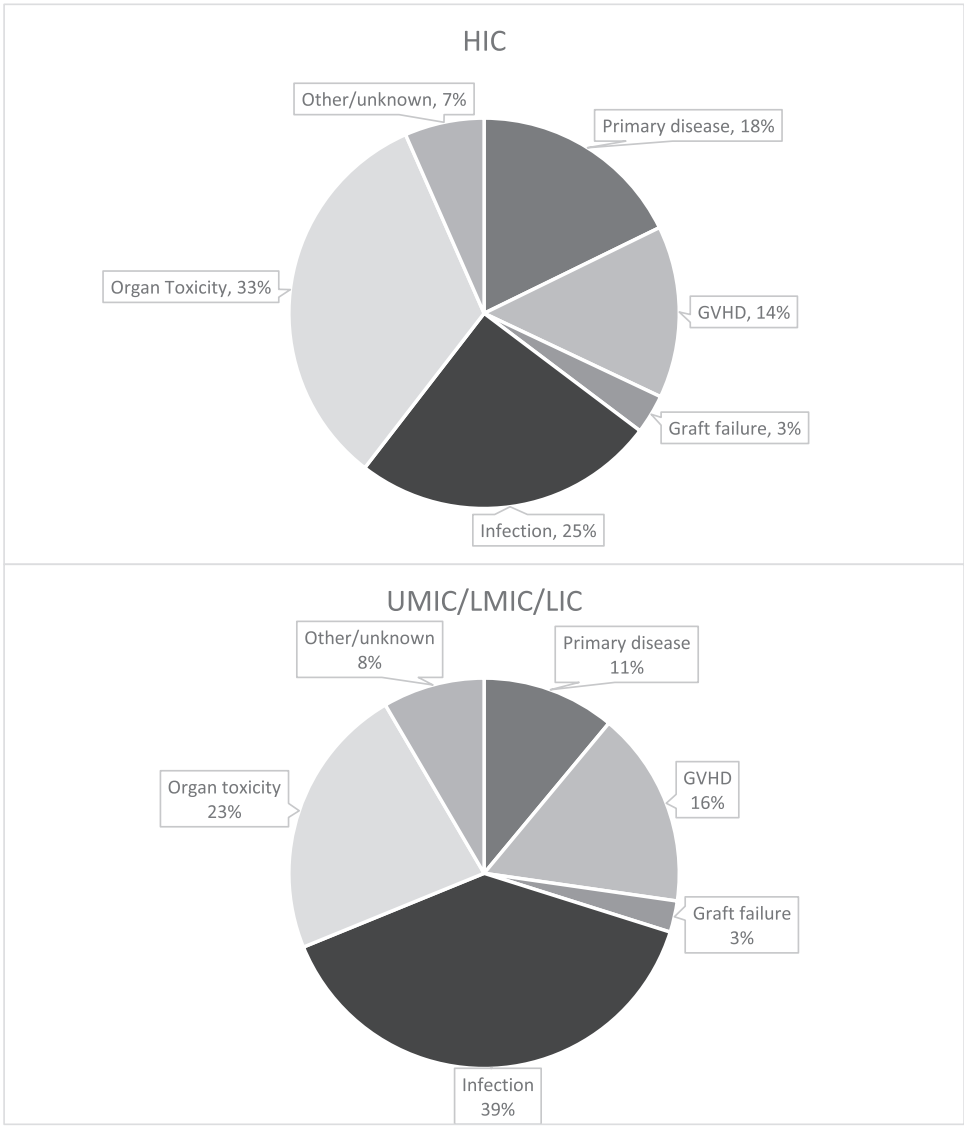


Figure 3. Causes of death by country-level GNI grouping.

States and across countries [6-9,24-26], and this variability may reflect underlying economic conditions. It is possible that care delivery factors may have contributed to the high proportion of deaths from infections that were seen in HMIC/LMIC/LIC settings (Figure 3). Standards exist for HCT center accreditation, such as those provided by the Foundation for Accreditation of Cellular Therapy and the JACIE, but the association of accreditation status with survival outcomes in registry analyses has been inconsistent [27,28]. There may be additional factors directly related to care delivery in the HCT and early post-HCT period that are linked with survival and require further study. Alternatively, it is possible that macroeconomic indicators are correlated with other factors that are related to post-HCT survival outcomes, such as training, experience, or staffing models in centers within lower economic settings. On a patient level, some have argued that lower socioeconomic settings may be associated with adverse outcomes influenced by immunologic mechanisms related to chronic stress [29]. We were not able to investigate these issues with our dataset. Last, it is possible that we may be seeing a phenomenon of delayed mortality related to economic settings. Patients treated in lower-resourced settings may not have the same level of intensive care support as do patients treated in higher resourced settings, leading to higher rates of early death after early post-HCT complications. Whether these patients could have been rescued in other settings or whether these patients may have had only modest life prolongation with intensive support in higher resourced settings is not known.

We acknowledge several limitations to our analysis. We did not have access to certain specific treatment- or disease-related variables, such as minimal residual disease (MRD). Country level macroeconomic variables do not necessarily reflect the local economic settings of specific transplant centers within these countries, or the characteristics of patients within these countries who have sufficient resources to access a transplant, relative to the rest of the population within these countries. We were unable to investigate local conditions surrounding specific individual centers using our dataset. Additional economic contextual information about patients receiving transplants in the specific centers included in this analysis would help us to better understand

the relationship between country-level macroeconomic factors and local transplant outcomes. Because we did find associations between country-level macroeconomic factors and 100-day transplant outcomes after adjusting for patient- and disease-related variables, we think that further studies of local economic contextual information and local health care delivery factors will be important to better understand the mechanism for our findings.

Further, our dataset contains limited detail related to post-HCT care provided across all of the international centers included in our analysis, which constrains our ability to draw conclusions about the mechanism for our findings. We were also limited by an absence of reporting from other centers within the countries included in our analysis, raising questions about the representativeness of our included centers, and potentially decreasing the robustness and generalizability of our findings. For those centers that were included, we were unable to investigate center volume or center experience within this dataset. Another important overall limitation is that we were only able to explain a proportion of the variance in outcomes with the variables that we included. We were unable to discern the contribution of other unmeasured variables or chance to our findings. Additionally, though longer-term outcomes would have been of interest to analyze, the completeness of reporting across centers and countries beyond day 100 prevented our ability to perform longer term analyses. This was unfortunate, as long-term disease-free survival and overall survival are the outcomes of most interest to patients and providers. Hopefully, our findings at day 100 will represent a call to action for international consortia to prioritize follow-up data collection to facilitate international studies with relevant, long-term outcomes.

We envision several next steps for this work. First, we urge a concerted effort to expand international data reporting from transplant centers worldwide and enhanced coordination between the existing transplant registries to facilitate future studies. As our study specifically investigated ALL, future work should also determine if our findings are consistent across other diseases. Attention should be directed to nonmalignant conditions, in particular, as these represent leading indications for transplantation for adults in developing countries [30]. Further, additional investigation is needed to determine the mechanism for our findings, to identify opportunities for potential interventions to improve outcomes. For example, because infection represented a high proportion of deaths in lower resourced settings, approaches to prevention, identification, and management of post-transplant infectious complications in these settings may be useful. For infection as well as other complications, lessons from other transplant centers may prove helpful. A recent successful pilot of a secure, online web-based clinical case sharing platform demonstrated the feasibility of knowledge transfer across economic settings in HCT [31]. Perhaps these and other interventions could be useful for new and emerging transplant programs [32].

In the current environment, with large and ongoing efforts supporting precision medicine in hematologic malignancies by including detailed patent, donor and disease specific factors relevant to transplantation outcomes [33], it is important to explore, in parallel, the contributions of center and country specific economic factors to outcomes. Collecting more detailed information regarding transplant outcomes on a global level would provide a great benefit to future research efforts. We have found that country-level macroeconomic indicators predict 100-day survival in alloHCT for ALL, but more work will need to be done to better understand these findings and to determine if similar findings are observed with long-term disease-free and overall survival. HCT may serve as a model for global collaborative cancer registries to identify international disparities in survival and to improve cancer outcomes for all patients.

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SUPPLEMENTARY DATA

Supplementary data related to this article can be found online at doi:10.1016/j.bbmt.2018.03.016.

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