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Analysis

Association of Outcomes and Socioeconomic Status in Mexican Patients Undergoing Allogeneic Stem Cell Transplantation



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The association of clinical outcomes after hematopoietic stem cell transplantation (HSCT) with the patient's socioeconomic status (SES) remains controversial, with the majority of studies reported to date performed in developed countries. Data from low- and middle-income regions where the SES varies greatly remain scarce. The objective of this study was to associate SES with outcomes after allogeneic HSCT in a referral center in Mexico. A retrospective study was performed including 124 consecutive patients. Patients were dichotomized into 2 groups based on a consensus with the Department of Social Work: low SES (level I-II) and high SES (level \geq III). Most patients were of low SES ($n = 84$; 68%). Age, educational attainment, employment status, and financial support were the sociodemographic characteristics that statistically differed between the 2 groups. All patients with low SES received financial support from governmental agencies or nongovernmental organizations (NGOs). Nonrelapse mortality and overall survival were similar in the 2 groups. Our study found no statistically significant differences in survival outcomes between patients of low SES and high SES. This demonstrates that our HSCT approaches are standardized and that all patients can benefit from HSCT irrespective of their financial status. It also suggests that the good outcomes in patients with low SES probably are related to the substantial governmental, NGO, and/or institutional subsidies these patients receive.

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INTRODUCTION

Worldwide, allogeneic hematopoietic stem cell transplantation (allo-HSCT) is widely used as a therapeutic approach to treat hematologic diseases. The associated morbidity and mortality remain concerns, however. In this context, numerous factors, mostly clinical characteristics, are associated with outcomes after allo-HSCT. Some patient and donor demographic variables have been reported to have a prognostic impact as well [1]. For almost 2 decades, patient socioeconomic status (SES) has been associated with outcomes in cancer [2]. SES is a variable related to economic and educational advantages or disadvantages that must be accounted for given the possible interference with education regarding treatment and compliance, as has been described in cancer patients treated in different medical settings. More recently, associations between disparities, such as ethnicity and SES, have been demonstrated, accounting for differences in health behaviors, limited resources, and poor access [3]; however, the association of SES and clinical outcomes after HSCT

remains controversial. Some studies have reported worse long-term outcomes in patients of low SES [1,3,4], whereas other studies have not found any SES-based differences in overall survival (OS), nonrelapse mortality (NRM), or other clinical variables [5].

However, these studies were performed in developed countries, and data from low- and middle-income regions where the SES varies greatly remain scarce. For instance, healthcare services in Mexico correspond to employment status, and, more importantly, health insurance is limited, and thus procedures such as HSCT are difficult to fund. Public institutions provide healthcare coverage for formally employed citizens. In this context, public healthcare plans (excluding universal healthcare, “Seguro Popular”) is provided through the Mexican Social Security Institute (IMSS, by its Spanish acronym; a tripartite system funded equally by the employee, the private employer, and the federal government) or to local, state, and federal government employees by the Institute for Social Security and Services for State Workers (ISSSTE by its Spanish acronym). In some scenarios, state governments provide independent healthcare services. Healthcare delivered through private insurance is available only to those who can afford it.

The National Institute of Medical Sciences and Nutrition Salvador Zubiran, located in Mexico City, is nationally renowned for its expertise in treating a wide variety of hematologic disorders using HSCT. Currently, there are approximately 12 centers in

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Mexico (including governmental institutions for formal employees and private hospitals) that perform HSCT in adults. Nonetheless, our institution, as a National Institute of the Mexican Ministry of Health, functions as a tertiary care hospital, receiving patients (with and without public/private insurance) from all over the country. Drawing on the heterogeneous patient population attending our institution, the objective of this study was to associate low SES and high SES with outcomes such as NRM, graft-versus-host disease (GVHD), and OS after allo-HSCT.

METHODS

Patients and Data

This retrospective study included 124 consecutive patients undergoing allogeneic and haploidentical HSCT at the National Institute of Medical Sciences and Nutrition Salvador Zubiran between May 1999 and March 2018. Demographic and clinical characteristics were obtained from a prospectively created HSCT database or retrospectively from institutional medical records.

HSCT

For steady-state bone marrow and granulocyte colony-stimulating factor (G-CSF)-primed bone marrow, hematopoietic stem cells were collected from donors by multiple aspirations of the iliac crests, in an operating room, under spinal anesthesia; for the latter, G-CSF (10 $\mu\text{g}/\text{kg}/\text{day}$) was administered for 4 days (every 8 hours), 3 days before the procedure and the day of the collection. Peripheral blood stem cells were collected by apheresis with previous mobilization with G-CSF; cells were harvested on days 4 and 5 of mobilization. Most patients with hematologic malignancies received reduced BUCY2 (busulfan 12 mg/kg orally and cyclophosphamide 80 mg/kg i.v.) [6], a reduced-intensity conditioning regimen developed at our center, and the rest received another myeloablative conditioning regimen. Patients with aplastic anemia received a cyclophosphamide-based conditioning regimen and/or antithymocyte globulin. Methotrexate (MTX) and cyclosporine A (CsA) were given for GVHD prophylaxis. MTX was administered i.v., 15 mg/m² on day +3 and 10 mg/m² on days +6 and +11. No patient received MTX on day +1 [7]. CsA was administered i.v., 1.5 mg/kg/12 hours, during day –1 and adjusting according to serum levels (200 to 300 ng/ μL) until 2005; afterward, CsA was administered orally (i.v. presentation was withdrawn from the market), 10 mg/kg during day –1 and 5 mg/kg starting on day 0, adjusting according to therapeutic monitoring. CsA was maintained for 4 months post-transplantation (8 months in aplastic anemia), and was subsequently reduced weekly (10%), until suspended, unless GVHD occurred. Antimicrobial prophylaxis and supportive therapy were given according to institutional guidelines. Patients were discharged when engraftment occurred and in the absence of infections or complications and follow-up was performed in the outpatient clinic. Modifications in the international guidelines for some medications (immunosuppression, conditioning regimen, and antibiotic prophylaxis) have been made owing to the better results observed in our experience, limited resources, or supply problems [8].

Financial Support

As we reported previously [9], the median costs (inpatient and 2-month outpatient follow-up) for autologous and allo-HSCT were 12,155 and 18,260 USD, respectively. Since 2002, the NGO “Unidos” has provided financial assistance for medications such as chemotherapeutic, immunosuppressive, and other expensive drugs (mostly antibiotics) not available or not provided by our institution [10]. On the other hand, the costs of hospitalization and associated expenses (supportive care, consultations, laboratory and imaging tests, among others), as well as outpatient consultations, have been subsidized according to an assigned institutional socioeconomic status classification ranging from I to VII (See Endpoints and Definitions below for further description), corresponding to payments on behalf of the patient of 7%, 16%, 36%, 57%, 77%, 100%, and 115% of the total cost, respectively. However, since 2015, hospitalization and all associated expenses (along with most of the medications if available at the institutional pharmacy) have been covered by the Catastrophic Expenses Protection Fund (“Seguro Popular”) for Mexicans without any other governmental healthcare (IMSS, ISSSTE, state healthcare) or private insurance. In this instance, for example, before 2015, a patient classified as level III would have paid 36% of the total cost of hospitalization and associated expenses, and our institution, through the Health Ministry, would have covered the remaining 64%; the chemotherapeutic drugs would have been fully or partially subsidized by “Unidos”. However, if the same patient underwent HSCT after 2015, the procedure would have been free of charge for the patient, covered by the “Seguro Popular”.

Endpoints and Definitions

SES was established according to the classification assigned by the Department of Social Work (levels I to VII). The institutional classification of SES is calculated and assigned based on standardized national guidelines and

a validated electronic platform, obtaining different percentages (ranging from 13% to 100%) for the following 5 variables: monthly family income (monthly wage divided by number of economic dependents) (55%); living conditions (type of housing, urban or rural area, number of bedrooms, facilities, and services) (20%); occupation of the main family provider (unemployment, formal or informal employment, retirement) (10%); monthly family expenses (total expenses \times 100, divided by total income) (10%); and family health condition (number of sick members, diagnoses, treatment time) (5%).

SES Level	Percentage
I	13–24
II	25–36
III	37–52
IV	53–68
V	69–84
VI	85–100
VII	Private health insurances or external institutional agreements

For this study, patients were dichotomized into 2 SES groups based on a consensus with the Department of Social Work: low (I–II) and high (\geq III). Patients in the low SES group are at a socioeconomic disadvantage, have the lowest income and poorest living conditions, and can afford to pay less than one-sixth (7%–16%) of their actual healthcare costs.

Employment status was considered as formal employment (salaried or contract employee), informal employment (freelance or merchant without tax obligations), or unemployment. Financial support was classified as universal healthcare (“Seguro Popular”), NGO (“Unidos”) or private, other governmental insurance, or none.

The Disease Risk Index was classified as low, intermediate, or high using standard definitions [11], and a Hematopoietic Cell Transplantation-Specific Comorbidity Index score was assigned to each patient. GVHD was evaluated according to National Institutes of Health guidelines. Endpoints included OS and NRM.

Statistical Analysis

Patient and HSCT characteristics are reported using descriptive statistics. Variables with normal distribution were compared using the independent *t* test or 1-way analysis of variance. Categorical variables were compared using the chi-square test or Fisher’s exact test. For acute and chronic GVHD, death and relapse without GVHD were considered competing risks. Patients at risk to develop acute or chronic GVHD excluded those with 30- and 100-day mortality, respectively. For the multivariate analysis, Cox regression was used to examine variables affecting NRM and OS. A *P* value of $<.05$ was considered significant. All statistical analyses were performed using SPSS version 21 (IBM, Armonk, NY).

RESULTS

The characteristics of 124 consecutive patients undergoing allogeneic and haploidentical HSCT, divided by low and high SES, are shown in Table 1. Most patients had a low SES ($n = 84$; 68%). Sociodemographic characteristics that statistically differed between the 2 groups included age, place of residence, educational attainment, employment status, and financial support. Patients in the low SES group were younger compared with those of high SES (median, 27.5 versus 41 years; $P = .001$). The most common place of residence among patients with low SES were other states (including the State of Mexico) (73%), contrasting with the majority of patients with high SES living in Mexico City (55%) ($P = .002$). Significantly more patients with high SES had a bachelor’s degree (45% versus 12%; $P < .001$). Formal employment was lower in the low SES group ($P < .001$); the NGO (“Unidos”) financed up to 70% of the patients with low SES, and the remaining 30% were financed by the universal healthcare “Seguro Popular”, compared with only 32% financed by either within the group with high SES ($P < .001$).

Although there were differences in diagnoses between the 2 groups ($P = .008$), with more acute leukemias and aplastic anemias in the low SES group, and more non-Hodgkin lymphomas and chronic myelogenous leukemias in the high SES

Table 1
Demographic and Clinical Characteristics (N = 124)

Characteristic	Low SES (Levels I-II)	High SES (Level ≥III)	P Value
Total, n	84	40	<.001
Age, yr, median (range)	27.5 (17-58)	41 (16-63)	.001
Sex, n (%)			.30
Male	50 (59)	20 (50)	
Female	34 (41)	20 (50)	
Underlying disease, n (%)			.008
Aplastic anemia	21 (25)	4 (10)	
Acute lymphoblastic leukemia	25 (30)	7 (17)	
Acute myeloblastic leukemia	9 (11)	6 (15)	
Chronic myelogenous leukemia	6 (7)	10 (25)	
Hodgkin disease	2 (2)	1 (2)	
Myelodysplastic syndrome	13 (15)	6 (15)	
Non-Hodgkin lymphoma	0	3 (8)	
Others	8 (9)	3 (8)	
HCT-CI, n (%)			.50
Low	63 (75)	26 (65)	
Intermediate	18 (21)	13 (33)	
High	3 (4)	1 (2)	
DRI (malignancies), n (%)			.08
Low	5 (6)	10 (25)	
Intermediate	37 (44)	17 (42)	
High	13 (15)	7 (17)	
Very high	1 (1)	1 (2)	
N/A (benign diseases)	28 (33)	5 (12)	
Type of HSCT, n (%)			.09
Allogeneic	77 (92)	40 (100)	
Haploidentical	7 (8)	0	
Conditioning regimen, n (%)			.30
Myeloablative	4 (5)	0	
Reduced-intensity	59 (70)	33 (83)	
Nonmyeloablative	21 (25)	7 (17)	
Place of residence, n (%)			.002
Mexico City	23 (27)	22 (55)	
State of Mexico	25 (30)	12 (30)	
Other states	36 (43)	6 (15)	
Educational attainment, n (%)			<.001
Elementary-high school	70 (83)	21 (53)	
Bachelor and above	10 (12)	18 (45)	
None	4 (5)	1 (2)	
Employment status, n (%)			<.001
Formal employment	4 (5)	15 (38)	
Informal employment	17 (20)	5 (12)	
Unemployment	63 (75)	20 (50)	
Marital status, n (%)			.20
Married	27 (32)	18 (45)	
Other	57 (68)	22 (55)	
Financial support, n (%)			<.001
Universal healthcare ("Seguro Popular")	25 (30)	2 (5)	
NGO ("Unidos")	59 (70)	11 (27)	
Private insurance/other governmental/none	0	27 (68)	
GVHD, n (%)			.80
Acute	21 (25)	11 (27)	

(continued)

Table 1 (Continued)

Characteristic	Low SES (Levels I-II)	High SES (Level ≥III)	P Value
Chronic	34 (40)	12 (30)	.20

HCT-CI, Hematopoietic Cell Transplantation-Specific Comorbidity Index; DRI, Disease Risk Index; N/A, not applicable.

group, there was no difference in the Disease Risk Index between the 2 groups ($P = .08$). This pattern was also observed in the Hematopoietic Cell Transplantation-Specific Comorbidity Index score ($P = .5$). There were no differences in acute or chronic GVHD incidence between the 2 groups ($P = .8$ and $.2$, respectively).

For the total cohort, 30-day, 100-day, and 1-year NRM were 3.2%, 8.8%, and 14.5%, respectively. As shown in Table 2, the overall NRM was similar in the low SES and high SES groups (18% versus 15%; $P = .9$). OS was 53% in the low SES group and 57% in the high SES group. In a multivariate (adjusted) Cox regression analysis performed for the entire cohort ($n = 124$), none of the analyzed sociodemographic and clinical characteristics was a statistically significant factor for higher NRM or worse OS. There were no statistically significant differences in

NRM and OS between the low SES and high SES groups ($P_{\text{Cox}} = .6$ and $.5$, respectively) (Figure 1).

DISCUSSION

HSCT is an expensive procedure [12] and even though the cost is substantially lower in countries like Mexico [9], it still represents a financial challenge for most patients, especially when one-half of the population is vulnerable and lives in poverty. Numerous studies have suggested that SES influences health outcomes associated with cancer incidence and mortality [13]. In addition, various social and economic variables have been associated with outcomes after allogeneic HSCT. Data on the association between SES and outcomes from developing regions remain scarce, however. For example, although a large study performed in the United States by Baker et al [1] included Hispanic patients, the results did not show statistically significant differences compared with white patients, in contrast with findings of Karanth et al [14], who reported a higher NRM in non-Caucasian allo-HSCT candidates (SES was not evaluated). These dissimilarities highlight the varying conditions from one country of residence to another irrespective of race or ethnicity.

The only study associating SES with outcomes in a developing country, published by Silla et al [15] almost a decade ago, found that the poorest SES group was associated with a higher incidence of acute and chronic GVHD, better engraftment, higher NRM, and worse survival. Moreover, these Brazilian authors briefly mentioned that the lack of significant differences in race was likely explained by the fact that almost all the patients included in their study were of Caucasian descent [15]. In the present study, we found similar rates of acute and chronic GVHD, as well as NRM and OS in our low SES and high SES groups. This is the first study from Mexico analyzing the influence of SES on outcomes after allo-HSCT. Patients undergoing autologous HSCT were not considered given the extremely low NRM (1.5%; data not shown). Race was not considered as a variable in our study, given that most patients were "mestizos" (a race within the Hispanic population with a mixed ancestry of white European and Native American from Latin America).

Furthermore, no study, regardless of its inclusion of vulnerable populations, such as the report by Loberiza et al [16]

Table 2
Multivariate (Adjusted) Cox Regression Analysis of NRM and OS for the Entire Cohort (N = 124)

Factor	NRM*		OS†	
	HR (CI 95%)	P Value	HR (CI 95%)	P Value
Female sex	2.0 (.8-5.3)	.10	.9 (.5-1.5)	.60
Age ≥40	.9 (0-3.0)	.10	.7 (.4-1.3)	.30
Intermediate/high HCT-CI	.8 (.3-1.9)	.60	1.7 (.9-3.0)	.70
Intermediate/high/very high DRI‡	1.3 (.3-5.7)	.70	1.1 (.5-2.5)	.80
Place of residence: other states (not Mexico City)	.5 (.2-1.7)	.10	1.4 (.8-2.6)	.20
Myeloablative/reduced-intensity conditioning	2.9 (.6-12.7)	.20	1.9 (.9-4.0)	.90
Educational attainment: none-high school	3.1 (.8-12.6)	.10	1.8 (.8-4.0)	.10
Marital status: other (not married)	1.0 (.4-2.9)	.90	1.0 (.6-1.7)	.90
Unemployment/informal employment status	1.4 (.4-4.2)	.60	1.1 (.5-2.6)	.70
Universal healthcare/NGO financial support	1.4 (.5-3.8)	.50	1.1 (.6-2.1)	.70
Low SES	1.3 (.5-3.3)	.60	1.3 (.5-3.2)	.50

HR indicates hazard ratio; CI, confidence interval.
 * NRM was 18% for low SES and 15% for high SES.
 † OS was 53% for low SES and 57% for high SES.
 ‡ Malignancies.

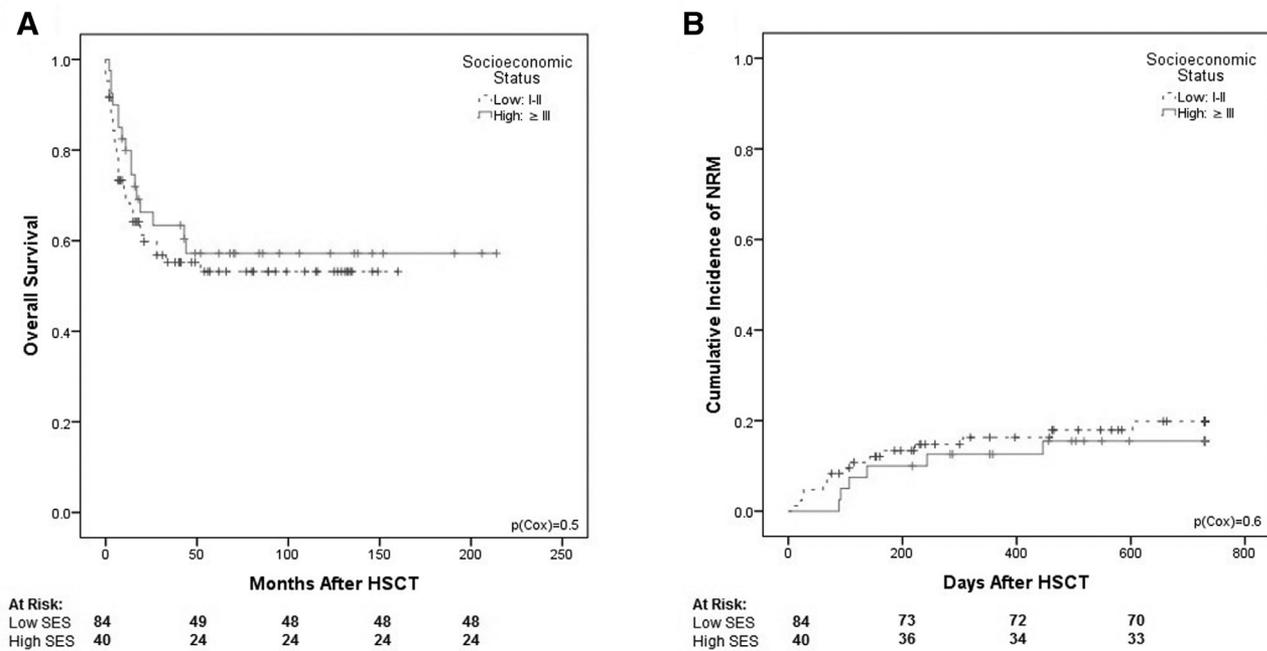


Figure 1. Clinical outcomes according to low and high SES for the entire cohort. (A) NRM. (B) OS.

comparing outcomes after HSCT by the place of residence (rural or urban areas), can accurately represent the entire panorama of a low- or middle-income country.

None of the sociodemographic (eg, place of residence, age, occupation) and clinical (eg, conditioning regimen) characteristics evaluated in the multivariate analysis was statistically associated with outcomes. Types of HSCT (allogeneic and haploidentical) were not compared owing to the small number of patients undergoing the latter.

SES varies among the Mexican population, but low SES predominates, along with unemployment and informal employment without access to most healthcare insurance [17,18]. Public and private healthcare plans operate independently, and access to them depends on work status and affordability.

On the other hand, the scarce availability of health workers, supplies, medications, and infrastructure (eg, hospitals,

beds), especially in the public sector, puts pressure on the healthcare system and impairs its potential to provide quality services [18]. Thus, although the universal healthcare plan “Seguro Popular” now covers approximately one-third of Mexico’s population, major problems remain. Mexico needs to build a more equitable, efficient, and sustainable health system [18].

At our institution, approximately 360 HSCTs have been performed (40% allogeneic) since the initiation of the consolidated HSCT program in November 1998. The aforementioned paucity in human and material resources has contributed to the low number of procedures performed. Nonetheless, the benefit of HSCT for each individual patient is always considered, and along with the NGO “Unidos” created in the early 2000s [10], we have ensured that outcomes remain similar irrespective of financial status.

We acknowledge some limitations of this study, including its retrospective nature and small cohort. However, because our institution is a referral center of the Mexican Health Ministry, it provides healthcare to a substantial, heterogeneous population, and thus this study can be considered a watershed to encourage larger studies from different developing countries to compare outcomes.

In conclusion, our study demonstrates were no statistically significant differences in NRM or OS between patients of low SES and high SES, demonstrating that our HSCT approaches are standardized and that all patients can benefit from HSCT irrespective of their financial status. It also suggests that the good outcomes in patients with low SES are likely related to the substantial governmental, NGO, and/or institutional subsidies that these patients receive.

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Conflict of interest statement: There are no conflicts of interest to report.

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