Transplantation and Cellular Therapy 29 (2023) 709.e1–709.e11

Transplantation and Cellular Therapy

journal homepage: www.astctjournal.org

ASTCT American Society for Transplantation and Cellular Therapy

Full Length Article
Analysis

Racial and Socioeconomic Disparities in Long-Term Outcomes in ≥1 Year Allogeneic Hematopoietic Cell Transplantation Survivors: A CIBMTR Analysis

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Financial disclosure: See Acknowledgments on page 709.e10.

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https://doi.org/10.1016/j.jtct.2023.07.013

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Article history:
Received 17 April 2023
Accepted 14 July 2023

Key words:
Allogeneic hematopoietic cell transplantation
Disparities
Socioeconomic status
Survival
Survivorship
Outcomes research

A B S T R A C T

Racial/ethnic minorities have demonstrated worse survival after allogeneic hematopoietic cell transplantation (HCT) compared to whites. Whether the racial disparity in HCT outcomes persists in long-term survivors and possibly may be even exacerbated in this population, which frequently transitions back from the transplant center to their local healthcare providers, is unknown. In the current study, we compared long-term outcomes among 1-year allogeneic HCT survivors by race/ethnicity and socioeconomic status (SES). The Center for International Blood and Marrow Transplant Research database was used to identify 5473 patients with acute myeloid leukemia, acute lymphocytic leukemia, chronic myeloid leukemia, or myelodysplastic syndromes who underwent their first allogeneic HCT between 2007 and 2017 and were alive and in remission for at least 1 year after transplantation. The study was restricted to patients who underwent HCT in the United States. SES was defined using patient neighborhood poverty level estimated from the recipient's ZIP code of residence; a ZIP code with ≥20% of persons below the federal poverty level was considered a high poverty area. The primary outcome was to evaluate the associations of race/ethnicity and neighborhood poverty level with overall survival (OS), relapse, and nonrelapse mortality (NRM). Cox regression models were used to determine associations of ethnicity/race and SES with OS, relapse, and NRM. Standardized mortality ratios were calculated to compare mortality rates of the study patients and their general population peers matched on race/ethnicity, age, and sex. The study cohort was predominately non-Hispanic white (n = 4385) and also included non-Hispanic black (n = 338), Hispanic (n = 516), and Asian (n = 234) patients. Overall, 729 patients (13%) resided in high-poverty areas. Significantly larger proportions of non-Hispanic black (37%) and Hispanic (26%) patients lived in high-poverty areas compared to non-Hispanic whites (10%) and Asians (10%) ($P < .01$). Multivariable analysis revealed no significant associations between OS, PFS, relapse, or NRM and race/ethnicity or poverty level when adjusted for patient-, disease- and transplantation-related covariates. Our retrospective cohort registry study shows that among adult allogeneic HCT recipients who survived at least 1 year in remission, there were no associations between race/ethnicity, neighborhood poverty level, and long-term outcomes.

INTRODUCTION

It has been shown racial/ethnic minorities and recipients residing in areas with higher neighborhood poverty levels and poorer community health status have worse survival after allogeneic hematopoietic cell transplantation (HCT) compared to whites and patients without socioeconomic adversity [1–5]. Such factors as race, socioeconomic status (SES), and healthcare insurance have been shown to influence decisions regarding stem cell transplantation [6]. There is limited information on variations in access to HCT in different patient populations. Recent literature has tried to break down some disparities that may affect access for patients needing HCT [2,7]. Identified barriers to access include age, sex, race, SES, and insurance status [8,9]. Even in this age of a growing geriatric oncology population, younger patients are still more likely to receive HCT [10]. With respect to sex, males are more likely than females to undergo HCT [11]. Studies also have shown that being uninsured or having Medicaid or Medicare insurance decreases the likelihood of undergoing HCT [12]. In addition to these factors, race has also been identified to significantly affect this outcome [10].

Survivorship care focuses on the patient beyond treatment period and provides long-term care after active treatment has ceased [13]. In HCT recipients, unique complications and therapy related events can occur even years after transplantation [14,15]. Many HCT patients are encouraged to maintain lifelong follow-up with a transplant center [16]. This can pose unique challenges for HCT survivors, such as monitoring for disease recurrence, presence of graft-versus-host disease (GVHD), and long-term chemotherapy-associated effects [17]. We chose the 1-year landmark because this is the typical time frame during which care is transitioned from the transplant center to community providers, especially patients without significant GHVD. Along with disease- and treatment-specific monitoring, survivorship can include assessment of quality of life, general health maintenance, and social and psychological adjustments after treatment [18]. Causes of death associated with transplantation include secondary malignancies, recurrent disease, infections, chronic GVHD, respiratory diseases, and cardiovascular diseases [19]. Given that racial minorities are more likely to have lower SES, these late effects from HCT may be accentuated in this vulnerable population [20]. Without resources to integrate back into society after HCT, many of these patients are lost to follow-up and do not follow the prescribed survivorship plan, which may drive worse outcomes [21].

A previous large Center for International Blood and Marrow Transplant Research (CIBMTR) study investigating the association of race/ethnicity and SES with outcomes of unrelated allogeneic HCT found that African American patients had worse overall survival (OS) after HCT compared to whites, and that African Americans and Hispanics had a higher cumulative incidence of nonrelapse mortality (NRM) compared to whites [5]. Recipients from the lowest SES quartile had worse OS and

higher NRM. Of note, the effects of race and SES on survival were independent of each other, and the inferior outcomes among African Americans could not be explained by transplantation-related factors or SES [22]. Survival was considered from the time of transplantation, and this study did not specifically focus on long-term HCT survivors who typically are no longer under the direct care of transplant centers and could be more prone to disparities in care and outcomes.

To address the gaps in the literature, our study investigated racial and SES outcome disparities in long-term allogeneic HCT survivors. We selected a representative multicenter cohort of survivors from the CIBMTR database who were in remission for at least 1 year after allogeneic HCT. We sought to (1) determine associations of ethnicity/race and neighborhood poverty level on survival in adult allogeneic HCT survivors with hematologic malignancies, (2) investigate the cumulative incidence of NRM and relapse post-transplantation by ethnicity/race and neighborhood poverty level in this patient population, and (3) compare standardized mortality ratios (SMRs) between our cohort and that of their age- and sex-matched peers in the general population.

METHODS

Data Source

The CIBMTR is a voluntary working group composed of nearly 500 transplantation centers worldwide that contribute detailed HCT data to a statistical center at the Medical College of Wisconsin in Milwaukee and the National Marrow Donor Program (NMDP) in Minneapolis. Participating centers are required to report all transplantations consecutively; compliance is monitored by onsite audits. Patients are followed longitudinally. Computerized checks for discrepancies, physician reviews 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 and are under the guidance of the Institutional Review Board of the NMDP.

Study Population

The study population consisted of first allogeneic HCT recipients from 2007 to 2017, age >18 years at transplantation who were alive and in remission ≥1 years from HCT with a diagnosis of acute myeloid leukemia, acute lymphoblastic leukemia, chronic myeloid leukemia, or myelodysplastic syndromes. The study was restricted to patients treated in the United States. All graft sources, donor sources, and conditioning regimens were considered. The CIBMTR database was used to identify 5473 patients who met the study selection criteria and included 4385 non-Hispanic white, 338 non-Hispanic black, 516 Hispanic, and 234 Asian patients. Other race/ethnicity groups, including American Indian/Alaskan Natives, Hawaiian/Pacific Islanders, and mixed race, were excluded because of the small number of patients in those categories to conduct meaningful analyses.

Statistical Analysis

The primary objective was to evaluate the association of race/ethnicity (non-Hispanic white (referent) versus non-Hispanic black versus Hispanic versus Asian) and neighborhood poverty level with OS, relapse, and NRM. Neighborhood poverty exposure was used to describe SES in our study and was defined according to the US Census definition as living in a high-poverty ZIP code, with high poverty level consisting of ≥20% of persons below the 100% federal poverty level [1]. OS was defined as the time from HCT to death from any cause. NRM was defined as the time from HCT to death without relapse, with relapse as a competing event. Relapse was defined as the time to recurrence of disease, with NRM as a competing event. Patients were censored at the date of last follow-up for all outcomes defined above. We also described the causes of death for our cohort.

Baseline characteristics were compared between racial and SES groups. OS was summarized using thew Kaplan-Meier method. Probabilities of NRM and relapse were calculated using the cumulative incidence function. A Cox proportional hazards regression model was used to evaluate the effect of the main variables of interest (race/ethnicity and neighborhood poverty level) on OS, NRM, and relapse after adjusting for demographic and disease variables. A significance level of .05 was used in our analyses.

The interaction between race/ethnicity and neighborhood poverty level was evaluated. Non-Hispanic white for race/ethnicity and low poverty level for SES were considered the referent groups for analyses. With these baseline groups, we had a sample size with the ability to detect a 10% difference in survival at 5 years among race/ethnicity groups, with 80% power and hazard ratio (HR) of .65.

Variables considered for inclusion into the model included race/ethnicity and poverty (main effects that are always kept in the model), age at transplantation, HCT Comorbidity Index (HCT-CI), insurance type, marital status, distance between residence and transplant center, location of residence (urban/rural), disease risk index at transplantation (low/intermediate/high/very high), year of transplantation, conditioning regimen, donor/graft type, GVHD prophylaxis, development of acute GVHD by 1 year post-HCT, and chronic GVHD by 1 year post-HCT. Center effect was accounted for via random effect with a lognormal distribution.

We also conducted analyses to estimate the SMRs for non-Hispanic whites, non-Hispanic blacks, and Hispanics comparing the number of observed deaths in our cohort to expected number of deaths within their age- and sex-matched general population controls in the United States. SMRs could not be estimated for Asians, because life tables for this racial group are not available through the National Center for Health Statistics. The SMR analysis was performed according to methods described in prior CIBMTR studies [23–26]. Analyses were performed using SAS statistical software (SAS Institute). All tests were 2-sided, and a .05 level of significance was used throughout the study.

RESULTS

Patient and Transplantation Characteristics

The characteristics of the study population by race/ethnicity are presented in Table 1. The median follow-up of survivors from 1 year post-HCT was 69 months for non-Hispanic whites, 50 months for non-Hispanic blacks, 59 months for Hispanics, and 57 months for Asians. There were significant differences in neighborhood poverty level by race with a greater proportion of non-Hispanic black (37%) and Hispanic (26%) recipients residing in high-poverty areas compared to non-Hispanic whites (10%) and Asians (10%) ($P < .01$). A significantly greater proportion of non-Hispanic white patients were privately insured compared to non-Hispanic black and Hispanic patients, who were more likely to be on Medicaid. Non-Hispanic whites also were significantly more likely to be married, to have a rural residence, and to live at a greater distance from the transplant center. There were significant differences in the 4 race/ethnicity cohorts by age at transplantation, sex,

Table 1
Characteristics of Adult Patients Undergoing First Allogeneic HCT for AML, ALL, CML, or MDS between 2007 and 2017 in the United States, and surviving 1-year after transplantation, by Race/Ethnicity

Characteristic	Non-Hispanic White	Non-Hispanic Black	Hispanic	Asian	*P* Value*
No. of patients	4385	338	516	234	
No. of centers	140	83	94	68	
Age at HCT, yr					<.01
Median (range)	55 (18-83)	47 (18-75)	41 (18-76)	47 (18-74)	
18-29 yr, n (%)	467 (11)	45 (13)	154 (30)	42 (18)	
30-39 yr, n (%)	469 (11)	62 (18)	92 (18)	44 (19)	
40-49 yr, n (%)	716 (16)	88 (26)	102 (20)	44 (19)	
50-59 yr, n (%)	1243 (28)	71 (21)	91 (18)	48 (21)	
60-69 yr, n (%)	1271 (29)	67 (20)	68 (13)	45 (19)	
≥70 yr, n (%)	219 (5)	5 (1)	9 (2)	11 (5)	
Recipient sex, n (%)					<.01
Male	2530 (58)	148 (44)	283 (55)	118 (50)	
Female	1855 (42)	190 (56)	233 (45)	116 (50)	
Neighborhood poverty level, n (%)†					<.01
Low	3937 (90)	214 (63)	383 (74)	210 (90)	
High	448 (10)	124 (37)	133 (26)	24 (10)	
Health insurance type, n (%)					<.01
Disability insurance ± others	103 (2)	10 (3)	8 (2)	6 (3)	
Private health insurance ± others	2889 (66)	181 (54)	251 (49)	144 (62)	
Medicaid ± others	420 (10)	85 (25)	171 (33)	40 (17)	
Medicare ± others	810 (18)	40 (12)	58 (11)	28 (12)	
Other	120 (3)	17 (5)	19 (4)	8 (3)	
Missing	43 (1)	5 (1)	9 (2)	8 (3)	
Highest level of education completed, n (%)					<.01
No primary	1 (0)	0 (0)	1 (0)	1 (0)	
Less than primary	2 (0)	1 (0)	4 (1)	1 (0)	
Primary	4 (0)	0 (0)	22 (4)	1 (0)	
Lower secondary	74 (2)	11 (3)	35 (7)	4 (2)	
Upper secondary	1015 (23)	110 (33)	164 (32)	37 (16)	
Postsecondary (vocational)	358 (8)	37 (11)	47 (9)	11 (5)	
Tertiary (4-yr degree)	1094 (25)	65 (19)	50 (10)	56 (24)	
Tertiary (2-yr degree)	235 (5)	18 (5)	26 (5)	14 (6)	
Advanced research degree	212 (5)	13 (4)	15 (3)	25 (11)	
Missing	1390 (32)	83 (25)	152 (29)	84 (36)	
Marital status, n (%)					<.01
Single, never married	626 (14)	96 (28)	161 (31)	41 (18)	
Married	3163 (72)	179 (53)	286 (55)	152 (65)	
Separated	47 (1)	8 (2)	12 (2)	4 (2)	
Divorced	356 (8)	32 (9)	35 (7)	12 (5)	
Widowed	105 (2)	7 (2)	8 (2)	8 (3)	
Missing	88 (2)	16 (5)	14 (3)	17 (7)	
Urban/rural residence, n (%)					<.01
Urban	3733 (85)	316 (93)	498 (97)	228 (97)	
Rural	652 (15)	22 (7)	18 (3)	6 (3)	
Distance between residence and transplant center, n (%)					<.01
<20 mi	1281 (29)	168 (50)	238 (46)	116 (50)	
20-50 mi	1045 (24)	52 (15)	106 (21)	60 (26)	
50-150 mi	1247 (28)	72 (21)	82 (16)	26 (11)	
> 150	812 (19)	46 (14)	90 (17)	32 (14)	
KPS at HCT, n (%)					<.01
<90	1569 (36)	133 (39)	140 (27)	75 (32)	
≥90	2738 (62)	201 (59)	370 (72)	155 (66)	
Missing	78 (2)	4 (1)	6 (1)	4 (2)	
HCT-CI at HCT, n (%)					<.01
0	1078 (25)	74 (22)	196 (38)	82 (35)	
1-2	1145 (26)	105 (31)	128 (25)	58 (25)	

(*continued*)

Table 1 (*Continued*)

Characteristic	Non-Hispanic White	Non-Hispanic Black	Hispanic	Asian	*P* Value*
≥3	1719 (39)	140 (41)	157 (30)	85 (36)	
Missing	443 (10)	19 (6)	35 (7)	9 (4)	
Disease, n (%)					<.01
AML	2225 (51)	172 (51)	222 (43)	125 (53)	
ALL	544 (12)	75 (22)	180 (35)	44 (19)	
CML	167 (4)	21 (6)	34 (7)	7 (3)	
MDS	1449 (33)	70 (21)	80 (16)	58 (25)	
Refined Disease Risk Index, n (%)					<.01
Low	307 (7)	27 (8)	56 (11)	21 (9)	
Intermediate	2347 (54)	204 (60)	286 (55)	151 (65)	
High	977 (22)	68 (20)	101 (20)	43 (18)	
Very high	60 (1)	5 (1)	11 (2)	1 (0)	
N/A; year of HCT <2008	457 (10)	18 (5)	41 (8)	8 (3)	
Missing, n (%)	237 (5)	16 (5)	21 (4)	10 (4)	
Donor type					<.01
HLA-identical sibling	1368 (31)	101 (30)	189 (37)	92 (39)	
Other related	357 (8)	99 (29)	84 (16)	31 (13)	
Well-matched unrelated (8/8)	1972 (45)	40 (12)	93 (18)	46 (20)	
Partially matched unrelated (7/8)	317 (7)	34 (10)	56 (11)	18 (8)	
Mismatched unrelated (≤6/8)	16 (0)	1 (0)	3 (1)	3 (1)	
Cord blood	355 (8)	63 (19)	91 (18)	44 (19)	
Graft type, n (%)					<.01
Bone marrow	631 (14)	49 (14)	73 (14)	29 (12)	
Peripheral blood	3399 (78)	226 (67)	352 (68)	161 (69)	
Cord blood	355 (8)	63 (19)	91 (18)	44 (19)	
Conditioning intensity, n (%)					<.01
MAC	2636 (60)	232 (69)	373 (72)	158 (68)	
RIC/NMA	1737 (40)	105 (31)	140 (27)	76 (32)	
Missing	12 (0)	1 (0)	3 (1)	0 (0)	
TBI use, n (%)					<.01
No	2791 (64)	158 (47)	248 (48)	114 (49)	
Yes	1582 (36)	179 (53)	265 (51)	120 (51)	
Missing	12 (0)	1 (0)	3 (1)	0 (0)	
GVHD prophylaxis, n (%)					<.01
PTCy + other(s)	307 (7)	86 (25)	71 (14)	32 (14)	
PTCy alone	12 (0)	0 (0)	1 (0)	0 (0)	
Tac + MMF ± other(s) (except PTCy)	817 (19)	64 (19)	68 (13)	20 (9)	
Tac + MTX ± other(s) (except MMF, PTCy)	2149 (49)	115 (34)	228 (44)	101 (43)	
Tac + other(s) (except MMF, MTX, PTCy)	312 (7)	13 (4)	55 (11)	25 (11)	
Tac alone	110 (3)	12 (4)	13 (3)	6 (3)	
CsA + MMF ± other(s) (except PTCy)	368 (8)	31 (9)	55 (11)	38 (16)	
CsA + MTX ± other(s) (except MMF, PTCy)	211 (5)	10 (3)	17 (3)	9 (4)	
CsA + other(s) (except MMF, MTX, PTCy)	20 (0)	1 (0)	2 (0)	0 (0)	
CsA alone	16 (0)	1 (0)	4 (1)	1 (0)	
Other(s)	42 (1)	1 (0)	1 (0)	1 (0)	
Missing	21 (0)	4 (1)	1 (0)	1 (0)	
Year of HCT, n (%)					<.01
2007	457 (10)	18 (5)	41 (8)	8 (3)	
2008	592 (14)	36 (11)	64 (12)	17 (7)	
2009	578 (13)	30 (9)	61 (12)	25 (11)	
2010	449 (10)	39 (12)	53 (10)	26 (11)	
2011	311 (7)	17 (5)	38 (7)	19 (8)	
2012	324 (7)	19 (6)	44 (9)	15 (6)	
2013	486 (11)	29 (9)	56 (11)	30 (13)	
2014	420 (10)	27 (8)	42 (8)	17 (7)	
2015	324 (7)	44 (13)	47 (9)	26 (11)	
2016	244 (6)	45 (13)	40 (8)	29 (12)	
2017	200 (5)	34 (10)	30 (6)	22 (9)	

(*continued*)

Table 1 (*Continued*)

Characteristic	Non-Hispanic White	Non-Hispanic Black	Hispanic	Asian	*P* Value*
Acute GVHD grade II-IV, n (%)					.44
No	2521 (57)	214 (63)	290 (56)	142 (61)	
Yes	1837 (42)	122 (36)	223 (43)	91 (39)	
Missing	27 (1)	2 (1)	3 (1)	1 (0)	
Chronic GVHD before 1 yr, n (%)					.76
No	1904 (43)	144 (43)	219 (42)	102 (44)	
Yes	2447 (56)	193 (57)	290 (56)	130 (56)	
Missing	34 (1)	1 (0)	7 (1)	2 (1)	
Follow-up of survivors from 1 yr post-HCT, mo, median (range)	69 (0-138)	50 (0-133)	59 (0-133)	57 (0-130)	

KPS, Karnofsky Performance Status; HCT-CI, Hematopoietic Cell Transplantation Comorbidity Index; AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; CML, chronic myeloid leukemia; MDS, myelodysplastic syndrome; MAC, myeloablative conditioning; RIC/NMA, reduced-intensity/nonmyeloablative conditioning; TBI, total body irradiation; PTCy, post-transplantation cyclophosphamide; MMF, mycophenolate mofetil; Tac, tacrolimus; CsA, cyclosporine; MTX, methotrexate; N/A, not applicable.

* Hypothesis testing: Pearson chi-square test.

† High-poverty neighborhood defined as ≥20% of persons living below the 100% federal poverty level; low-poverty neighborhood defined as <20% of persons below the 100% federal poverty level.

Karnofsky Performance Status at transplantation, HCT-CI at transplantation, diagnosis, Disease Risk Index, donor type, graft type, conditioning regimen intensity, use of total body irradiation, GVHD prophylaxis, and year of transplantation.

Table 2 present the characteristics of our cohort by neighborhood poverty level. The median follow-up of survivors for both low- and high-poverty areas was 62 months. As noted above, a significantly greater proportion of non-Hispanic

Table 2
Characteristics of Adult Patients Undergoing First Allogeneic HCT for AML, ALL, CML, or MDS Between 2007 and 2017 in the United States and surviving 1-year after transplantation, by Neighborhood Poverty Level*

Characteristic	Low Poverty	High Poverty	*P* Value
No. of patients	4744	729	
No. of centers	142	106	
Age at HCT, yr			<.01
Median (range)	54 (18-83)	50 (18-76)	
18-29 yr, n (%)	585 (12)	123 (17)	
30-39 yr, n (%)	562 (12)	105 (14)	
40-49 yr, n (%)	808 (17)	142 (19)	
50-59 yr, n (%)	1285 (27)	168 (23)	
60-69 yr, n (%)	1281 (27)	170 (23)	
≥70 yr, n (%)	223 (5)	21 (3)	
Recipient sex, n (%)			.15
Male	2687 (57)	392 (54)	
Female	2057 (43)	337 (46)	
Race, n (%)			<.01
Non-Hispanic white	3937 (83)	448 (61)	
Non-Hispanic black	214 (5)	124 (17)	
Hispanic	383 (8)	133 (18)	
Asian	210 (4)	24 (3)	
Health insurance type, n (%)			<.01
Disability insurance ± others	114 (2)	13 (2)	
Private health insurance ± others	3076 (65)	389 (53)	
Medicaid ± others	533 (11)	183 (25)	
Medicare ± others	820 (17)	116 (16)	
Other	139 (3)	25 (3)	
Missing	62 (1)	3 (0)	
Highest level of education completed, n (%)			<.01
No primary	3 (0)	0 (0)	
Less than primary	6 (0)	2 (0)	
Primary	17 (0)	10 (1)	
Lower secondary	95 (2)	29 (4)	
Upper secondary	1122 (24)	204 (28)	
Post-secondary (vocational)	391 (8)	62 (9)	
Tertiary (4-yr degree)	1138 (24)	127 (17)	
Tertiary (2-yr degree)	258 (5)	35 (5)	
Advanced research degree	234 (5)	31 (4)	
Missing	1480 (31)	229 (31)	
Marital status, n (%)			<.01
Single, never married	752 (16)	172 (24)	
Married	3347 (71)	433 (59)	
Separated	50 (1)	21 (3)	
Divorced	368 (8)	67 (9)	
Widowed	106 (2)	22 (3)	
Missing	121 (3)	14 (2)	
Urban/rural residence, n (%)			<.01
Urban	4190 (88)	585 (80)	
Rural	554 (12)	144 (20)	
Distance between residence and transplant center, n (%)			<.01
<20 mi	1574 (33)	229 (31)	
20-50 mi	1181 (25)	82 (11)	
50-150 mi	1187 (25)	240 (33)	
>150 mi	802 (17)	178 (24)	
KPS, n (%)			.92
<90	1666 (35)	251 (34)	
≥90	2999 (63)	465 (64)	
Missing	79 (2)	13 (2)	
HCT-CI, n (%)			.34
0	1232 (26)	198 (27)	
1-2	1263 (27)	173 (24)	
≥3	1818 (38)	283 (39)	
Missing	431 (9)	75 (10)	
Disease, n (%)			<.01

(*continued*)

Table 2 (*Continued*)

Characteristic	Low Poverty	High Poverty	*P* Value
AML	2371 (50)	373 (51)	
ALL	700 (15)	143 (20)	
CML	192 (4)	37 (5)	
MDS	1481 (31)	176 (24)	
Refined Disease Risk Index, n (%)			.54
Low	358 (8)	53 (7)	
Intermediate	2582 (54)	406 (56)	
High	1043 (22)	146 (20)	
Very high	68 (1)	9 (1)	
N/A; year of HCT<2008	443 (9)	81 (11)	
Missing	250 (5)	34 (5)	
Donor type, n (%)			<.01
HLA-identical sibling	1515 (32)	235 (32)	
Other related	482 (10)	89 (12)	
Well-matched unrelated (8/8)	1913 (40)	238 (33)	
Partially matched unrelated (7/8)	350 (7)	75 (10)	
Mismatched unrelated (≤6/8)	19 (0)	4 (1)	
Cord blood	465 (10)	88 (12)	
Graft type, n (%)			.10
Bone marrow	671 (14)	111 (15)	
Peripheral blood	3608 (76)	530 (73)	
Cord blood	465 (10)	88 (12)	
Conditioning intensity, n (%)			.75
MAC	2937 (62)	462 (63)	
RIC/NMA	1793 (38)	265 (36)	
Missing	14 (0)	2 (0)	
TBI use, n (%)			.80
No	2878 (61)	433 (59)	
Yes	1852 (39)	294 (40)	
Missing	14 (0)	2 (0)	
GVHD prophylaxis, n (%)			.83
PTCy + other(s)	417 (9)	79 (11)	
PTCy alone	12 (0)	1 (0)	
Tac + MMF ± other(s) (except PTCy)	827 (17)	142 (19)	
Tac + MTX ± other(s) (except MMF, PTCy)	2261 (48)	332 (46)	
Tac + other(s) (except MMF, MTX, PTCy)	354 (7)	51 (7)	
Tac alone	124 (3)	17 (2)	
CSA + MMF ± other(s) (except PTCy)	433 (9)	59 (8)	
CSA + MTX ± other(s) (except MMF, PTCy)	214 (5)	33 (5)	
CSA + other(s) (except MMF, MTX, PTCy)	20 (0)	3 (0)	
CSA alone	19 (0)	3 (0)	
Other(s)	39 (1)	6 (1)	
Missing	24 (1)	3 (0)	
Year of HCT, n (%)			.25[†]
2007	443 (9)	81 (11)	
2008	600 (13)	109 (15)	
2009	617 (13)	77 (11)	
2010	496 (10)	71 (10)	
2011	340 (7)	45 (6)	
2012	350 (7)	52 (7)	
2013	529 (11)	72 (10)	
2014	440 (9)	66 (9)	
2015	372 (8)	69 (9)	
2016	313 (7)	45 (6)	
2017	244 (5)	42 (6)	
Acute GVHD grade II-IV, n (%)			.19[†]
No	2727 (57)	440 (60)	
Yes	1986 (42)	287 (39)	
Missing	31 (1)	2 (0)	
Chronic GVHD before 1 yr, n (%)			.74
No	2044 (43)	325 (45)	
Yes	2662 (56)	398 (55)	
Missing	38 (1)	6 (1)	
Follow-up of survivors from 1 yr post-HCT, mo, median (range)	62 (0-138)	62 (0-134)	

[*] High-poverty neighborhood defined as ≥20% of persons living below the 100% federal poverty level; low-poverty neighborhood defined as <20% of persons below the 100% federal poverty level.

[†] Hypothesis testing with the Pearson chi-square test.

blacks and Hispanics live in high-poverty neighborhoods. As expected, a greater number of recipients residing in low-poverty neighborhoods were significantly more likely to have private health insurance, be married, have an urban residence, and live closer to the transplant center. Among disease- and transplantation-related characteristics, significant differences between the 2 cohorts were noted in age at transplantation, diagnosis, and donor type.

Analysis by Race/Ethnicity

Table 3 and Figure 1 highlights outcomes at the 1-year post-transplantation time point. There was a significant difference in OS at 5 years with highest survival in Asian recipients (74%), followed by Hispanic (70%), non-Hispanic white (65%) and non-Hispanic black (65%) patients ($P = .003$). There was no difference in the cumulative incidence of relapse, although the cumulative incidence of NRM mirrored that of OS, with the lowest rates in Asians (13%), followed by Hispanics (16%), non-Hispanic blacks (20%), and non-Hispanic whites (21%) ($P = .002$). However, in multivariable analyses adjusting for patient-, disease-, and transplantation-related characteristics, there was no difference in OS or NRM between the 4 race/ethnicity groups (Table 4). Of note, significant associations were noted between urban/rural place of residence and insurance status and OS and NRM. Recipients with rural residence have higher risks of overall mortality (HR, 1.22 versus urban residence; 95% CI, 1.08 to 1.38; $P = .002$) and NRM (HR, 1.33; 95% CI, 1.13 to 1.57; $P = .0005$). Compared to patients with private health insurance, the risk of overall mortality was higher in patients on Medicaid (HR, 1.17; 95% CI, 1.01 to 1.35; $P = .033$) and patients on Medicare (HR, 1.22; 95% CI, 1.07 to 1.39; $P = .0029$), although this association was observed only in Medicare recipients for NRM (HR, 1.25; 95% CI, 1.06 to 1.48; $P = .008$). There was no association between residence location or insurance status with the risk of relapse. The causes of death were similar in all 4 groups, with disease relapse the most common cause followed by GVHD, infections, and organ failure.

Table 3
Univariate Analysis for 5-Year Outcomes, by Race/Ethnicity and Neighborhood Poverty Level

Outcomes*		OS		Relapse		NRM	
	N	Probability, % (95% CI)	*P* Value	Probability, % (95% CI)	*P* Value	Probability, % (95% CI)	*P* Value
Race/ethnicity							
Non-Hispanic white	4385	65 (64-66)	.003	20 (19-21)	.218	21 (19-22)	.002
Non-Hispanic black	338	65 (59-70)		23 (19-28)		20 (15-25)	
Hispanic	516	70 (65-74)		21 (17-25)		16 (13-20)	
Asian	234	74 (67-80)		19 (14-25)		13 (9-18)	
Neighborhood poverty level†							
Low	4744	66 (65-68)	.156	20 (18-21)	.108	20 (19-21)	.653
High	729	62 (58-66)		23 (20-26)		20 (17-23)	

* Outcome estimates are from 1 year post-transplantation.
† High-poverty neighborhood defined as ≥20% of persons living below the 100% federal poverty level; low-poverty neighborhood defined as <20% of persons below the 100% federal poverty level.

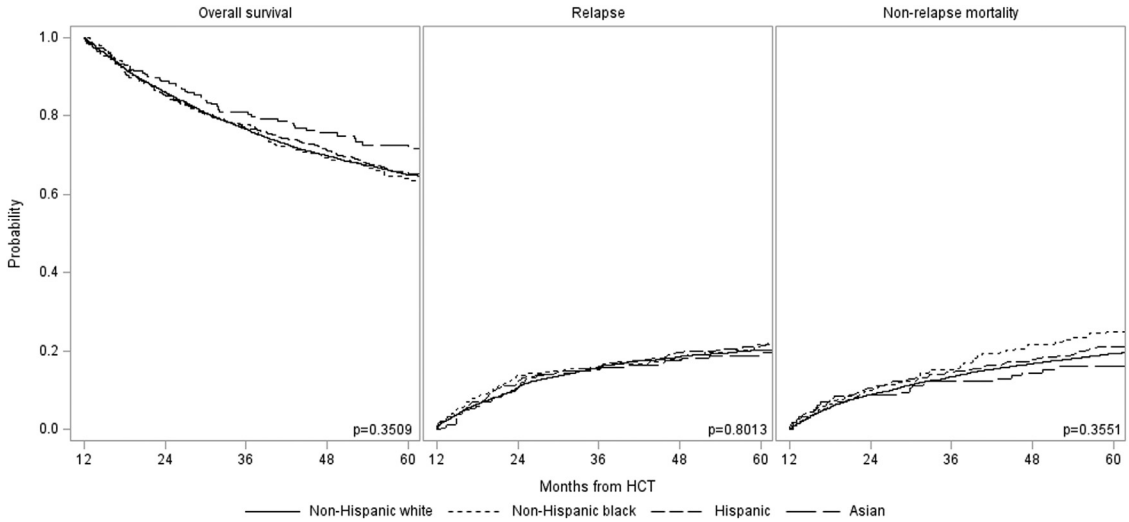

Figure 1. Long-term outcomes in adult allogeneic HCT survivors with acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), chronic myeloid leukemia (CML), and myelodysplastic syndromes (MDS) who survived in remission for ≥1 year by race/ethnicity. (A) OS. (B) Relapse. (C) NRM.

Table 4
Results of Multivariable Analysis

Outcome	OS*			Relapse†			NRM‡		
	N	HR (95% CI)	*P* Value	N	HR (95% CI)	*P* Value	N	HR (95% CI)	*P* Value
Race/Ethnicity									
Non-Hispanic white	4385	1.00	.3509	4385	1.00	.8013	4373	1.00	.3551
Non-Hispanic black	338	1.16 (.95-1.41)	.1433	338	1.10 (.86-1.41)	.4418	338	1.24 (.95-1.62)	.1226
Hispanic	516	1.01 (.84-1.20)	.9500	516	1.05 (.85-1.30)	.6601	515	1.04 (.82-1.32)	.7570
Asian	234	.89 (.69-1.15)	.3636	234	.94 (.69-1.27)	.6818	234	.87 (.61-1.25)	.4488
Neighborhood poverty level§									
Low	4744	1.00	.1184	4744	1.00	.1251	4732	1.00	.8299
High	729	1.11 (.97-1.26)		729	1.14 (.96-1.36)		728	1.02 (.86-1.21)	

* Other variables significantly associated with OS included age at HCT, sex, acute GVHD, chronic GVHD by 1 year post-transplantation, conditioning regimen intensity, donor type, Disease Risk Index, HCT Comorbidity Index, insurance type, rural/urban residence, and year of HCT.
† Other variables significantly associated with relapse included acute GVHD, chronic GVHD by 1 year post-transplantation, conditioning regimen intensity, donor type, Disease Risk Index, and year of HCT.
‡ Other variables significantly associated with NRM included age at HCT, sex, acute GVHD, chronic GVHD by 1 year post-transplantation, donor type, graft type, HCT Comorbidity Index, GVHD prophylaxis, insurance type, rural/urban residence, and year of HCT. Thirteen patients who had received post-transplantation cyclophosphamide as GVHD prophylaxis were excluded from the multivariable analysis for NRM because they did not have any events.
§ High-poverty neighborhood defined as ≥20% of persons living below the 100% federal poverty level; low-poverty neighborhood defined as <20% of persons below the 100% federal poverty level.

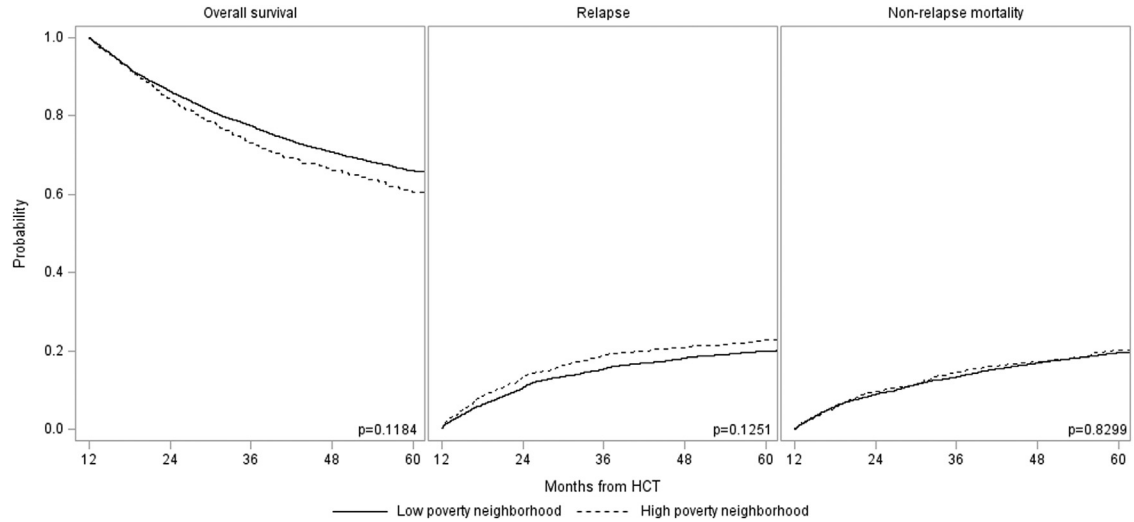

Figure 2. Long-term outcomes in adult allogeneic HCT survivors with AML, ALL, CML, and MDS who survived in remission for ≥1 year by neighborhood poverty level. (A) OS. (B) Relapse. (C) NRM.

Analysis by Neighborhood Poverty Level

Tables 3 and 4 also show results for univariate and multivariable analysis by neighborhood poverty level. In univariate analysis, there was no difference in 5-year OS, relapse, or NRM between patients coming from low- and high-poverty neighborhoods Figure 2. This was confirmed in multivariable analyses, which again did not show any significant differences in the risks of OS, relapse, or NRM among the 2 groups. As noted above, residence location and insurance status were associated with OS and NRM.

Mortality Rates Compared to the General Population

The analysis comparing observed versus expected mortality for non-Hispanic white, non-Hispanic black, and Hispanic recipients is shown in Table 5. Our cohort of 1-year HCT survivors had mortality rates approximately 10-fold higher than their age- and sex-matched controls from the general population. We also observed differences by race/ethnicity, with Hispanic recipients having higher mortality rates (SMR, 19.2) than non-Hispanic whites (SMR, 10.0) and non-Hispanic blacks (SMR, 11.2).

DISCUSSION

In our study of adult allogeneic HCT recipients with hematologic malignancies who had survived in remission for ≥1 year, we observed no differences in OS, relapse, or NRM by either race/ethnicity or neighborhood poverty levels. Previous CIBMTR studies that have considered HCT recipients from the time of transplantation have demonstrated significant differences in survival by race/ethnicity, neighborhood poverty level, and community health status [1,3,5]. We had hypothesized that these disparities would persist or even be accentuated in long-term survivors, because many patients frequently transition back to their local healthcare ecosystem after the first 3 to 6 months following transplantation, where the systemic racial and socioeconomic disparity factors may be prevalent in their communities. Previously recognized disparities in the outcomes of allogeneic HCT are once again evidenced by the differences in OS and NRM seen in this study. However, these differences in OS and NRM among various racial/ethnic groups become less pronounced when adjusted for other risk factors. These findings may suggest that those differences are related to the variability in certain patient and treatment characteristics of different racial/ethnic groups.

We postulate several hypotheses for our observed lack of association between race/ethnicity, neighborhood poverty level, and outcomes in long-term HCT survivors seen after accounting for other risk factors and sociodemographic characteristics. First, patients from minority groups who are able to receive allogeneic transplantation are not representative of the universe of racial/ethnic and socioeconomically disadvantaged populations. For example, HCT recipients have been reported to have higher literacy levels, education status, and SES than the general population [8,27,28]. Thus, HCT survivors who transition back to their communities may have different and better healthcare access and experience than their peers in the general population. Second, a substantial portion of mortality occurs in the first year following allogeneic HCT, where the impact of healthcare disparities may be the most significant. In addition, a larger proportion of racial minority patients lived closer to their transplant center and may have

Table 5
Standardized Mortality Ratios for Non-Hispanic White, Non-Hispanic Black, and Hispanic Patients Compared to Their Age- and Sex-Matched General Population Controls

Population	N	Person-yr	Observed	Expected	SMR (95% CI)	P Value
All patients	5239	23,346	2074	198.6	10.4 (10.0-10.9)	<.0001
Non-Hispanic white	4385	19,950	1791	179.2	10.0 (9.5-10.5)	<.0001
Non-Hispanic black	338	1254	124	11.1	11.2 (9.3-13.3)	<.0001
Hispanic	516	2142	159	8.3	19.2 (16.4-22.5)	<.0001

had the advantage of closer follow-up by their treating institution. For example, among non-Hispanic whites, 53% lived within 50 miles of the transplant center, and 15% reported a rural place of residence. In contrast, a greater proportion of racial/ethnic minority recipients lived close to the transplant center (65% of non-Hispanic blacks, 66% of Hispanics, and 66% of Asians lived within 50 miles) or in an urban area (7%, 3%, and 3%, respectively, reported rural residence). It is also important to note that our study cohort consisted of patients who underwent HCT in the contemporary era when there is an emphasis on providing systematic post-transplantation survivorship care, routine utilization of social workers to assess and provide psychosocial support to patients and their families, and increased availability of financial and other support services from patient advocacy organizations. These factors might have mitigated the adverse effect of healthcare disparity factors in long-term HCT survivors. Additionally, the use of newer GVHD prevention strategies, such as post-transplantation cyclophosphamide may have contributed, as evidenced by comparable rates of acute and chronic GVHD among the 4 racial groups despite the greater use of donors other than HLA-identical siblings or matched unrelated donors in racial minorities.

In a related single center study of allogeneic and autologous HCT $\geq$1 year survivors, Joo et al. also did not find any association between post-transplant survival and community health status – a measure that was previously reported to significantly influence 1-year survival [3,29]. It is well recognized that healthcare disparities is a complex construct, and as supported by our analysis, other related factors such as insurance status and neighborhood poverty level may be the mechanism for adverse outcomes previously reported among minority HCT recipients.

An important finding from our study that has immediate application in clinical practice is the observation of mortality risks that are ~10 times higher for non-Hispanic whites and non-Hispanic blacks and ~20 times higher for Hispanics. This is consistent with other studies that have shown higher rates of mortality in allogeneic HCT survivors than what would be expected in the general population up to at least 10 to 15 years post-transplantation [24,30-32]. Our study did show worse mortality for the Hispanic population, which we postulate is due to health-related factors associated with decreased survival other than the primary malignancy. More work is needed to understand why this minority community continues to show worsening mortality. Our findings underscore the importance of continued lifelong vigilance for late complications of transplantation with screening, prevention, and prompt management according to published guidelines [14,15,17]. There also is a need to develop care models and infrastructure, such as survivorship care plans, telemedicine, and web-based self-management applications, that can facilitate the care of long-term survivors who may not be under the direct care of their transplant centers [27,33-35].

Some limitations of our study must be considered. First, the study is limited because of its retrospective registry-based design. As noted earlier, we cannot address the totality of healthcare disparities in transplantation, given that our study population consisted of patients who were able to undergo allogeneic HCT, and we have no mechanism of identifying patients who needed a transplant but could not receive one. It is also possible that we are underestimating the true representation of long-term care for HCT survivors. Although we had a very robust median follow-up, it is still possible that longer follow-up may be needed to reveal differences in late effects that manifest much later post-transplantation. Our findings are applicable only to the United States and are not generalizable to other countries.

In summary, we found that among adult allogeneic HCT recipients who survived for at least 1 year in remission, there were no significant differences in OS, relapse, or NRM based on race/ethnicity or neighborhood poverty level. HCT survivors have significantly higher risks of mortality compared to the general population and require long-term monitoring and prevention of late effects irrespective of race/ethnicity or SES.

ACKNOWLEDGMENTS

Financial disclosure: The CIBMTR is supported primarily by Public Health Service U24CA076518 from the National Cancer Institute (NCI), the National Heart, Lung and Blood Institute (NHLBI) and the National Institute of Allergy and Infectious Diseases (NIAID); HHSH250201700006C from the Health Resources and Services Administration (HRSA); and N00014-20-1-2705 and N00014-20-1-2832 from the Office of Naval Research; Support is also provided by Be the Match Foundation, the Medical College of Wisconsin, the National Marrow Donor Program, and from the following commercial entities: AbbVie; Accenture; Actinium Pharmaceuticals, Inc.; Adaptive Biotechnologies Corporation; Adienne SA; Allovir, Inc.; Amgen, Inc.; Astellas Pharma US; bluebird bio, inc.; Bristol Myers Squibb Co.; CareDx; CSL Behring; CytoSen Therapeutics, Inc.; Daiichi Sankyo Co., Ltd.; Eurofins Viracor; ExcellThera; Fate Therapeutics; Gamida-Cell, Ltd.; Genentech Inc; Gilead; GlaxoSmithKline; Incyte Corporation; Janssen/Johnson & Johnson; Jasper Therapeutics; Jazz Pharmaceuticals, Inc.; Karyopharm Therapeutics; Kiadis Pharma; Kite, a Gilead Company; Kyowa Kirin; Magenta Therapeutics; Medac GmbH; Merck & Co.; Millennium, the Takeda Oncology Co.; Miltenyi Biotec, Inc.; MorphoSys; Novartis Pharmaceuticals Corporation; Omeros Corporation; Oncopeptides, Inc.; Orca Biosystems, Inc.; Pfizer, Inc.; Pharmacyclics, LLC; Sanofi Genzyme; Seagen, Inc.; Stemcyte; Takeda Pharmaceuticals; Tscan; Vertex; Vor Biopharma; Xenikos BV.

Conflict of interest statement: **B. Blue:** Consultancy: *Janssen*, Pfizer, Abbvie, *Oncopeptides.* **W. Wood:** Research Funding: *Pfizer*; Consultancy: *Tedadoc*; Consultancy and Current equity holder in publicly traded company: *Koneksa Health*. **N. Majhail:** Consultancy: *Incyte Corporation, Anthem, Inc.*. All other authors reported no conflict of interest.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jtct.2023.07.013.

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