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Original Article

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Ethnic Disparities in Allogeneic Hematopoietic Cell Transplantation: A Secondary CIBMTR Study

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Abstract

Background: Allogeneic Hematopoietic Cell Transplantation (allo-HCT) is a necessary therapeutic option for patients with Acute Myeloid Leukemia (AML) and Acute Lymphoblastic Leukemia (ALL). This study aims to evaluate the effects of race on the outcomes of allo-HCT.

Methods: This secondary data analysis utilized the Center for International Blood and Marrow Transplant Research (CIBMTR) data repository for allo-HCT cases in the United States from 2008 to 2018. The eligible patients were aged 18 or older, undergoing initial allo-HCT for AML or ALL from an HLA-identical sibling or 8/8 matched unrelated donor. Recipient, disease, and transplant variables were assessed. A Cox proportional hazards model was employed for multivariable analysis.

Results: The dataset included 4,783 cases, with 4,310 White, 211 Black, 230 Asian, 12 Native Hawaiian/Pacific Islander, and 26 American Indian/Alaska Native individuals. Asians had a significantly higher mortality rate when receiving transplants from HLA-identical siblings compared to well-matched unrelated donors (76.56 *vs*. 41.91%, p=0.001). The median survival times did not differ significantly among the racial and ethnic groups. White (39.08 months), Black or African American (25.16 months), Asian (62.27 months), Native Hawaiian or other Pacific Islanders (25.33 months), and the overall estimated median survival across all groups was 39.14 months (log rank test p=0.870). After adjusting for age, disease type, and donor type, Black or African American individuals had a 25.2% higher risk of death compared to White individuals (HR: 1.252 95%CI: (1.043, 1.503) p=0.016).

Conclusion: This study reveals significant disparities in outcomes among different racial and ethnic groups

Keywords: Acute myeloid leukemia, Cancer, Ethnicity, Hematopoietic cell transplantation, Race

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Introduction

Allogeneic Hematopoietic Cell Transplantation (allo-HCT) is a critical medical procedure for individuals with various hematological disorders, including leukemia and lymphoma. However, disparities in long-term outcomes after allogeneic HCT persist, with racial and socioeconomic factors playing a significant role. Research has shown that racial and ethnic minorities experience poorer survival rates after allo-HCT compared to their white counterparts, as shown in a study by Blue *et al* (1). Furthermore, the complexity of these disparities extends to a composite endpoint of survival without grade III-IV acute Graft-Versus-Host Disease (GVHD), known as graft-versus-host disease-free relapse-free survival (GRFS) (2).

Furthermore, an analysis of worldwide utilization of hematopoietic cell transplantation emphasizes the need for a global approach to address these disparities and the importance of addressing them on a global scale (3). Additionally, research by Wood *et al* showed how country-level macroeconomic indicators can predict variations in allogeneic transplant outcomes, emphasizing the role of socio-economic factors (4). This, in turn, indicates the need for ethnically diverse stem cell donors, underlining the importance of capturing the need for diverse HLA phenotypes to improve transplantation outcomes (5).

Several studies have explored the influence of race and ethnicity on the outcomes of allo-HCT. Sigmund's study highlights the pivotal role of allo-HCT in treating various malignant and nonmalignant conditions (6). Another study demonstrated different trends and outcomes associated with race in the context of hematopoietic cell transplantation (7). Additionally, literature suggests lower utilization rates of allogeneic hematopoietic stem cell transplant among Hispanic and Black populations (8). Baker's work categorizes patients by ethnicity and examines the impact on allogeneic hematopoietic cell transplantation outcomes (9). Landry's study, specifically addresses racial disparities in outcomes of hematopoietic stem cell transplantation, particularly in cases of acute or chronic leukemia (10). Collectively, these studies demonstrate significant disparities in allo-HCT outcomes based on race and ethnicity, indicating the need for further investigation into the underlying causes of these disparities. As research and healthcare practices evolve, it is crucial to consider and address these disparities, ultimately advancing our understanding of the complexities surrounding allo-HCT and striving for greater equity in the provision of this life-saving treatment. Therefore, we decided to conduct the present study with the aim of evaluating the effects of race on the outcomes of allo-HCT.

Materials and Methods

This was a secondary data analysis study on Center for International Blood and Marrow Transplant Research (CIBMTR) data repository on allo-HCT cases. Data were analyzed from the CIBMTR repository on individuals aged 18 years or older who underwent their first allo-HCT in the United States between 2008 and 2018 for either Acute Myeloid Leukemia (AML) or Acute Lymphoblastic Leukemia (ALL). Only patients who received transplants from HLA-identical siblings or 8/8 Matched Unrelated Donors (MUD) were included in this study. Data were obtained from the CIBMTR repository, which is publicly available for research purposes. The authors acknowledge CIBMTR as the data source and commit to citing them in any publications or presentations, as per their data use agreement (11).

In this study, various facets related to recipients, diseases, and transplant procedures were investigated. Recipient variables included age, categorized into groups spanning from 18 to 29 years up to 70 years and above. Sex was recorded as either male or female, while race encompassed options such as White, Black or African American, Asian, Native Hawaiian or other Pacific Islanders, American Indian or Alaska Native. We excluded cases with missing or mixed ethnicity data, as well as those with data indicating more than one ethnicity. Additionally, the Karnofsky/Lansky performance score was employed to gauge functional status, stratifying recipients into brackets of 90-100 (high functional status), below 90 (reduced functional status), or marked as missing. The disease-related variables were also examined, including the primary disease type, which was categorized as either AML or ALL. Furthermore, disease status at the time of Hematopoietic Cell Transplant (HCT) was categorized into Primary Induction Failure (PIF),

Complete Remission 1 (CR1), Complete Remission 2 (CR2), Greater than or equal to Complete Remission 3 (>=CR3), relapse, or marked as missing data. We evaluated transplant-related variables, including graft type, which was categorized as either bone marrow or peripheral blood. Donor type was categorized as HLA-identical Sibling or Well-matched Unrelated (8/8). In addition, outcome variables, including the occurrence of events (such as transplant-related complications) and censoring, as well as the duration of follow-up in months from HCT to the last follow-up for each recipient were examined. A total of 157 cases were excluded due to missing or mixed ethnicity data.

Statistical analyses

Descriptive results were presented using frequencies and proportions for categorical variables, such as ethnicity, age group, and disease type. The demographic characteristics of the study population were summarized using tables and figures to provide an overview of the data distribution. Chi-square tests were used to examine the association between categorical variables, such as ethnicity and disease type, and ethnicity and Karnofsky performance score. Fisher's exact test was used to analyze the association between ethnicity and disease type when the expected cell count was less than 5. The statistical analysis was conducted using a Cox proportional hazards model to calculate hazard ratios for the given outcome variables. The analysis was performed using STATA MP/version 17 statistical software, with a significance level set at α=0.05. The assumptions of the Cox model, including the assumption of proportional hazards, were checked and met. The model included independent variables such as time from HCT to last follow-up, ethnicity, age group, and Karnofsky performance score.

Results

Among 4783 cases, there were 4310 individuals classified as White, 211 identified as Black or African American, 230 classified as Asian, 12 categorized as Native Hawaiian or other Pacific Islanders, and 26 individuals belonging to the American Indian or Alaska Native ethnicity. Within the White ethnicity, the proportion of males was higher, with 55.36%. In contrast, the Black or African American and American Indian or Alaska Native ethnicities had a slightly higher proportion of females than males, with 53.08% and 53.35% female, respectively. Asian and Native Hawaiian or other Pacific Islander ethnicities had a roughly equal distribution of males and females. Chi-square test demonstrates a statistically significant relationship between ethnicity and age group ($p<0.001$), showing the importance of considering these demographic factors in further analyses ($p=0.065$).

Table 1 presents demographic data on individuals categorized by ethnicity and age group. The White ethnicity constitutes the largest portion across all age groups, with a significant and greater number of subjects in the 50-59 and 60-69 age categories. Black or African American individuals also were numbers in count across most age groups, except for the 60-69 category where they have a lower proportion compared to other ethnicities. Asians, in contrast, show a comparatively smaller presence across all age groups. The chi-square test demonstrates a statistically significant relationship between ethnicity and age group ($p<0.001$), showing the importance of considering these demographic factors in further analyses.

The Native Hawaiian or other Pacific Islander ethnicities had the highest proportion of AML cases, accounting for 83.33% of cases in this group. This is followed by White individuals with AML at 80.39%, Asian individuals at 72.17%, Black or African American individuals at 73.46%, and American Indian or Alaska Native individuals at 69.23%. The chi-square test revealed a statistically significant relationship between disease type and ethnicity ($p=0.003$), suggesting that the distribution of diseases varies significantly across different ethnicities.

The Native Hawaiian or other Pacific Islander group had the highest proportion of individuals with high Karnofsky scores (90-100), at 83.33%, followed closely by the Asian group, at 61.3%. In contrast, the Black or African American group had the lowest proportion of individuals with high Karnofsky scores (90-100), at 61.66%.

Table 2 displays death rates (%) based on donor type in different ethnicities along with corresponding p values from Fisher's exact tests. For White and Black or African American individuals, Fisher's exact tests

Table 1. Univariable comparison of characteristics of subjects included in the study

		White	Black or African American	Asian	Native Hawaiian or other Pacific Islanders	American Indian or Alaska Native	p
No.		4310	211	230	12	26	-
Age groups	18-29	499(11.58%)	36(17.06%)	47(20.43%)	3(25%)	6(23.08%)	<0.001*
	30-39	497(11.53%)	25(11.85%)	41(17.83%)	0(0%)	5(19.23%)	
	40-49	812(18.84%)	51(24.17%)	44(19.13%)	2(16.67%)	1(3.85%)	
	50-59	1171(27.17%)	56(26.54%)	49(21.3%)	3(25%)	7(26.92%)	
	60-69	1106(25.66%)	35(16.59%)	42(18.26%)	4(33.33%)	7(26.92%)	
	70+	225(5.22%)	8(3.79%)	7(3.04%)	0(0%)	0(0%)	
Gender	Male	2386(55.36%)	99(46.92%)	115(50%)	6(50%)	12(46.15%)	0.065**
	Female	1924(44.64%)	112(53.08%)	115(50%)	6(50%)	14(53.85%)	
Disease	AML	3465(80.39%)	155(73.46%)	166(72.17%)	10(83.33%)	18(69.23%)	0.003**
	ALL	845(19.61%)	56(26.54%)	64(27.83%)	2(16.67%)	8(30.77%)	
Karnofsky performance score	90-100	2460(57.08%)	109(51.66%)	141(61.3%)	10(83.33%)	16(61.54%)	0.27*
	<90	1808(41.95%)	100(47.39%)	89(38.7%)	2(16.67%)	10(38.46%)	
	Missing	42(0.97%)	2(0.95%)	0(0%)	0(0%)	0(0%)	
Disease status at time of HCT	PIF	519(12.04%)	16(7.58%)	35(15.22%)	3(25%)	3(11.54%)	0.075**
	CR1	2695(62.53%)	136(64.45%)	141(61.3%)	7(58.33%)	18(69.23%)	
	CR2	738(17.12%)	37(17.54%)	40(17.39%)	1(8.33%)	2(7.69%)	
	>=CR3	38(0.88%)	8(3.79%)	3(1.3%)	0(0%)	0(0%)	
	Relapse	318(7.38%)	14(6.64%)	11(4.78%)	1(8.33%)	3(11.54%)	
	Missing	2(0.05%)	0(0%)	0(0%)	0(0%)	0(0%)	
Graft type	Bone marrow	697(16.17%)	28(13.27%)	41(17.83%)	1(8.33%)	2(7.69%)	0.452*
	Peripheral blood	3613(83.83%)	183(86.73%)	189(82.17%)	11(91.67%)	24(92.31%)	
Donor type	HLA-identical sibling	1415(32.83%)	107(50.71%)	94(40.87%)	7(58.33%)	9(34.62%)	<0.001*
	Well-matched unrelated (8/8%)	2895(67.17%)	104(49.29%)	136(59.13%)	5(41.67%)	17(65.38%)	

PIF: Primary Induction Failure, CR: Complete Remission, HCT: Hematopoietic Cell Transplantation

* Chi-square; **, Fisher's exact test,

Table 2. Death rate among different ethnicities based on the donor type

	HLA-identical sibling	Well-matched unrelated (8/8)	p
White	766(54.13)	1612(55.68)	0.845*
Black or African American	62(57.94)	61(58.65)	0.981*
Asian	49(76.56)	57(41.91)	0.001*
Native Hawaiian or other Pacific Islanders	3(42.86)	4(80)	0.001*
American Indian or Alaska Native	4(44.44)	7(41.18)	0.854*

* Fisher's exact test.

revealed no significant differences in death rates between those who received transplants from HLA-identical siblings and well-matched unrelated donors. However, for Asian and Native Hawaiian or other Pacific Islander individuals, significant disparities exist. For Asian individuals, Fisher's exact test demonstrated a significantly higher death rate when receiving transplants from HLA-identical siblings compared to well-matched unrelated donors (76.56 *vs.* 41.91%, p=0.001). Similarly, Native Hawaiian or other Pacific Islander individuals indicated a substantially higher death rate with well-matched unrelated donors compared to HLA-identical siblings (80 *vs.* 42.86%, p=0.001). But number of data was scarce for Native Hawaiian or other Pacific Islander individuals.

Among the groups examined, White individuals demonstrated a median survival of 39.08 months (95%CI: 35.92-43.65), while Black or African American individuals had a lower median survival of 25.16 months (95%CI: 15.82-37.63). Asians had the highest median survival time (62.27 months, 95%CI: 42.27-NE), although the upper limit of the confidence interval could not be estimated due to limited data. Native Hawaiian or other Pacific Islander individuals had a median survival time of 25.33 months (95%CI: 2.34-NE), although the upper limit of the confidence interval could not be estimated due to limited data. Unfortunately, there is insufficient data for American Indian or Alaska Native individuals. In total, encompassing all the racial and ethnic groups, the estimated median survival is 39.14 months (95%CI: 36.18-43.61). A log-rank test revealed no statistically significant difference in median survival times between ethnic groups (p=0.870), as shown in figure 1.

In the univariable, no racial or ethnic groups (Black or African American, Asian, Native Hawaiian or other Pacific Islander, and American Indian or Alaska Native) showed statistically significant differences in hazard compared to the White group (p>0.05). Adjusting for age groups, disease type, and donor type, compared to the White racial or ethnic group (which serves as the reference category with a hazard ratio of 1), individuals in the Black or African American group had a 25.2% higher hazard (risk) of experiencing the event of death (HR: 1.252 95%CI: (1.043, 1.503) p-value: 0.016). This analysis suggests that there is a statistically significant difference in hazard between the Black or African American group and the White group. The other racial or ethnic groups (Asian, Native Hawaiian or other Pacific Islander, and American Indian or Alaska Native) showed no statistically significant differences in hazard compared to the White group (Table 3).

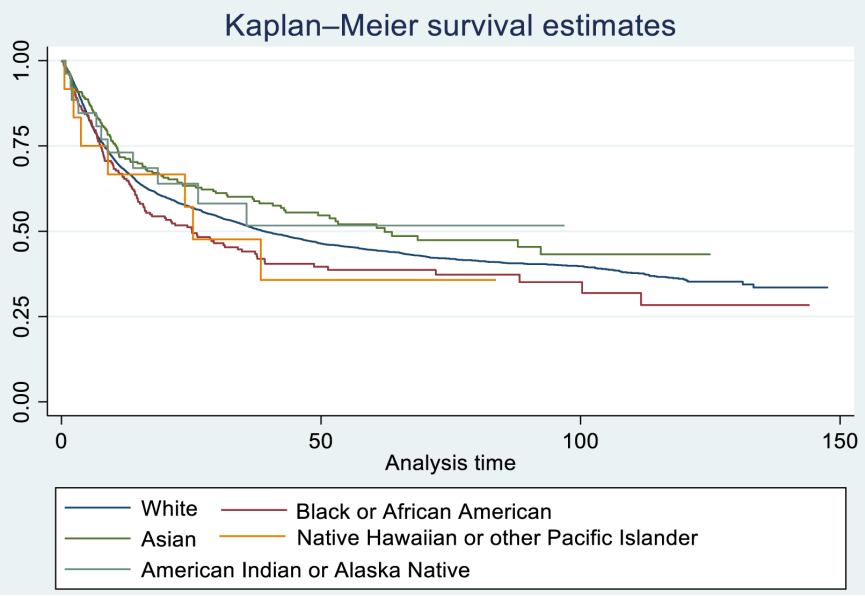

Figure 1. Median survival times between ethnic groups.

Table 3. Cox regression of the hazard of death in different ethnicities compared to Whites

	Univariable model b				Adjusted multivariable model for age groups, disease type, and donor type			
	HR	95%CI lower	Upper	p	HR	95%CI lower	Upper	p
White	Reference	-	-		Reference	-	-	-
Black or African American	1.13	0.987	1.961	0.217	1.252	1.043	1.503	0.016
Asian	0.63	0.438	1.013	0.067	0.89	0.732	1.082	0.244
Native Hawaiian or another Pacific Islander	1.45	0.834	2.541	0.193	1.268	0.603	2.666	0.533
American Indian or Alaska Native	0.794	0.512	1.207	0.053	0.93	0.514	1.682	0.815

Discussion

In this secondary study conducted by CIBMTR, the impact of race on the outcomes of allo-HCT was rigorously examined. The study encompassed a substantial sample size of 4,783 cases, within which 4,310 individuals were classified as White, 211 as Black or African American, 230 as Asian, 12 as Native Hawaiian or other Pacific Islanders, and 26 as American Indian or Alaska Native. The key findings of this investigation revealed compelling insights into the relationship between race and allo-HCT outcomes. One of the most striking observations pertains to the significantly higher death rate among Asian individuals who received transplants from HLA-identical siblings in comparison to well-matched unrelated donors, with a stark contrast of 76.56% versus 41.91%. This statistical disparity (p=0.001) indicates the critical importance of donor selection, particularly for Asian patients, in achieving successful transplant outcomes.

The findings indicate disparities in the chances of individuals getting a HCT based on their race. It suggests that White individuals have a higher likelihood of receiving HCT compared to African Americans. This inequality was consistent across all HCT types, including autologous, HLA-identical sibling, and unrelated donor transplants. These data also revealed that men were more likely to undergo HCT than women, with the gender difference being particularly significant in the case of autologous HCT (12,13).

In Garcia *et al*'s study (14), they pointed out some notable differences in how folks from different backgrounds fare after HSCT. It turns out, non-Hispanic Black patients tend to have better survival chances compared to non-Hispanic white and Hispanic patients. In this study, it was found that while the median survival times were consistent across racial and ethnic groups, a closer examination of donor types used in allo-HCT revealed differences in survival rates, particularly among Asian patients when receiving transplants from HLA-identical siblings compared to well-matched unrelated donors The median survival times varied across racial and ethnic groups, with White individuals at 39.08 months, Black or African American individuals at 25.16 months, Asian individuals at 62.27 months, and Native Hawaiian or other Pacific Islander individuals at 25.33 months. However, the log rank test revealed no statistically significant differences in survival times among the studied racial and ethnic categories (p=0.870). What is particularly intriguing, however, is when the data was adjusted for factors like age groups, disease type, and donor type. In this context, the study unveiled a 25.2% higher risk of death for individuals in the Black or African American group, as indicated by the hazard ratio of 1.252 and a 95% confidence interval from 1.043 to 1.503, with a p value of 0.016. This adjustment underscores the critical importance of taking these confounding

variables into account when evaluating the impact of race on allo-HCT outcomes. It suggests that while the initial survival statistics may not show significant differences, a deeper analysis reveals the influence of these variables on the ultimate outcomes for different racial and ethnic groups.

While Hamilton *et al* (15) found that race, in isolation, does not significantly affect survival outcomes post-HCT when adjusted for other factors. The current study found that after adjusting for multiple variables, Black or African American individuals had a 25.2% higher risk of death compared to other racial groups, as indicated by the hazard ratio of 1.252.

In contrast with the current study, Blue *et al* (1) primarily investigates long-term survival among 1-year allo-HCT survivors, encompassing a diverse patient population and considering neighborhood poverty levels. Their findings reveal no significant associations between race, socioeconomic status, and long-term outcomes, such as overall survival, progression-free survival, relapse, and nonrelapse mortality.

Khera *et al*'s (16) study found that survival rates were comparable between Non-Hispanic Whites (NHW) and racial/ethnic minority patients following allogeneic HCT, both before and after adjusting for various factors. In contrast, the present study identified significant disparities in death rates among different racial and ethnic groups in the context of different donor types used in allo-HCT. While Khera *et al*'s study suggests that uniform medical care can mitigate racial disparities, the current research highlights the specific influence of donor selection on survival outcomes within diverse racial backgrounds.

In contrast to this study, the Sigmund *et al's* study (6) identified no significant differences in outcomes for patients undergoing allo-HCT based on race or primary area of residence. This contrast is noteworthy, especially in the context of a prior study conducted by Mielcarek *et al* (17) which demonstrated a significant increase in mortality among Black patients undergoing allo-HCT compared to White patients. Mielcarek *et al* had suggested that this disparity might be linked to higher rates of severe aGVHD. While Mielcarek *et al* (17) reported significant differences, this study found significant disparities in death rates among different racial and ethnic groups, particularly among Asian patients, after adjusting for multiple variables. However, the present study's findings for White and Black patients were more comparable, aligning with the results of Sigmund *et al* (6), indicating the complexity of assessing the impact of race on allo-HCT outcomes and the need for an understanding of various contributing factors and covariates. This study has several limitations to consider. It relies on retrospective data from the CIBMTR, potentially introducing selection bias. Findings are specific to the United States between 2008 and 2018, limiting generalizability. The study primarily focuses on five racial and ethnic groups, which may not fully represent the diversity within these categories. These limitations highlight the need for further research to provide a more comprehensive understanding of allo-HCT outcomes in diverse settings.

Conclusion

In conclusion, this study showed the presence of significant disparities in allo-HCT outcomes across diverse racial and ethnic groups. This observation underscores the urgency of addressing healthcare disparities and ensuring equitable access to allo-HCT procedures for all patients. Further research and interventions are essential to mitigate these disparities and improve the overall effectiveness and fairness of allo-HCT in healthcare settings.

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Conflict of Interest

Authors declare no conflict of interest.

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