Race and Invasive Fungal Infection in Solid Organ Transplant Recipients

Amelia K. Boehme, MSPH; Gerald McGwin, MS, PhD; David R. Andes, MD; G. Marshall Lyon, MD; Tom Chiller, MD, MPH; Peter G. Pappas, MD; John W. Baddley, MD, MSPH

Health disparities in access to solid organ transplantation (SOT) and graft survival are well recognized, but there are limited data on the relationship of race to risk of invasive fungal infection (IFI) among SOT recipients. We conducted a case-control study using data from the Transplant-Associated Infection Surveillance Network (TRANSNET) to investigate race and IFI. Cases (n=1,214) and controls (n=16,550) were compared on demographic variables using chi-square, and the relationship between race and IFI was assesses with unconditional logistic regression. Compared to White transplant patients, Blacks had similar odds of developing IFI (OR=.97, 95% CI 0.82–1.15, P=.7125), while participants who identified as other ethnicity were less likely to develop IFI (OR=.56, 95% CI .41–.75, P<.001). Blacks, when compared to White patients, were at increased odds of developing cryptococcal infection (OR 2.19, 95%CI 1.35–3.54, P=.002). Despite pharmacogenetic differences, Black transplant recipients were not more likely overall to develop IFI compared to White transplant recipients. (*Ethn Dis*. 2014;24[3]:382–385)

Key Words: Invasive Fungal Infection, Solid Organ Transplant, Aspergillosis, Candidiasis, Cryptococcosis

Introduction

Health disparities in access to solid organ transplantation have been recognized for many years.[1–6] These disparities may be related to socioeconomic status, unfavorable geographic location, health beliefs, patient interest in transplantation, biologic factors or organ donation.[1,6] Resistance to organ donation among minorities is a significant impediment given that antibody matching is the primary determinant of organ allocation.[7] Thus, a predominantly White donor pool may place minorities at a distinct disadvantage with regard to transplant matching.[4,6,8]

In addition to decreased access to transplantation, there are also disparities in outcomes after solid organ transplantation. When compared with White kidney transplant recipients, Black recipients have decreased graft survival and increased rates of acute and chronic rejection.[2,4] In contrast, liver transplant recipients of Asian race have a survival advantage when compared to non-Asian groups.[9] Because increased rejection rates may lead to increased immunosuppression in some recipients, ethnic differences may exist in risk for post-transplant infection risk and outcomes.[4,10,11]

Infections, particularly invasive fungal infections (IFIs), are an important cause of morbidity and mortality in transplant recipients. Intensified immunosuppression and other factors may contribute to the increased risk of IFIs;[4,10] however, it is unclear if race is one of these factors because of the lack of data investigating this association. Herein, with use of data from the Transplant-Associated Infection Surveillance Network (TRANSNET), we investigated the association between race and IFI.

Intensified immunosuppression and other factors may contribute to the increased risk of invasive fungal infections;[4,10] however, it is unclear if race is one of these factors because of the lack of data investigating this association.

Materials and Methods

Study Participants

TRANSNET is a Centers for Disease Control and Prevention and pharmaceutical industry co-sponsored prospective surveillance network comprising 23 US transplant centers with University of Alabama at Birmingham serving as the coordinating center.[12,13] Enrollment of transplant recipients into this study occurred between March 2001 and October 2005. Incident cases of proven and probable invasive mycoses in transplant recipients were identified through March 2006, and data were collected using a standardized data collection form. Patients with proven or probable IFI, based on modified European Organization for Research and Treatment of Cancer/ Mycoses Study Group (EORTC/MSG) criteria,[14] were included in the case data set. The current analysis combines this dataset with a control data set that includes information on patients who received a transplant at one of the study sites but who were diagnosed with IFI during the study period. The control data set variables available included demographics, transplant center, type of transplant and underlying reason for transplantation. This study was approved by the Institutional Review Board of all participating institutions. Informed consent was ob-

From University of Alabama at Birmingham School of Public Health (AKB, GG); and University of Wisconsin (DRA); and Emory University School of Medicine (GML); and Centers for Disease Control (TC); and University of Alabama at Birmingham School of Medicine (PGP, JWB); and Birmingham VA Medical Center (JWB).

Address correspondence to John W. Baddley, MD, MSPH; University of Alabama at Birmingham; Division of Infectious Diseases; 1900 University Blvd, THT 229; Birmingham AL 35294-0006; 205.934.5191; 205.934.5155 (fax); jbaddley@uab.edu

tained where dictated by the participating institution.

Study Design and Variable Definitions

This study used an unmatched case-control design. A total of 1,214 cases of IFI were identified at the 23 centers. The exposure variable of interest, race, was classified as White, Black or other and was collected similarly for both cases and controls. Ethnicity was defined as Hispanic or Non-Hispanic. In addition, in the case data set, race was further classified into five groups (White, Black, Asian/Pacific Islander, American Indian/Alaska Native and other).

Statistical Analysis

Demographic characteristics were compared between cases and controls using chi-square and Student's t-test. Crude age and sex-adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for the association between race and IFI were calculated using unconditional logistic regression. To evaluate ORs for the association between race and specific IFI types, we used only the first IFI (for cases with multiple IFIs); controls were without IFI. All tests were two-sided and performed at the $\alpha = .05$ level.

Results

There were 1,214 cases and 16,550 controls in the solid organ transplantation (SOT) population. Cases and controls were predominantly White (77.5% and 83.4%, respectively) with mean age in the late 40s (Table 1). Cases were more likely than controls to be male (60.8% and 59.5%, respectively) than females (39.2% and 40.5%, respectively). There were significant differences between the cases and controls with regard to race, age and transplant type (Table 1). There is a higher percentage of liver transplants in the case group and a higher percentage of kidney transplants in the control group ($P<.0001$). Case patients were less likely to be classified as Black or other when compared to control patients ($P<.001$).

Table 1. Patient characteristics

Variable	Controls		Cases		*P*
	n	%	*n*	%	
Age	47.5	SD 15.1	49.8	SD 14.9	<.001
Sex					.380
Male	9982	60.8	713	59.5	
Female	6436	39.2	485	40.5	
Race					<.001
White	12629	77.5	968	83.4	
Black	2525	15.5	145	12.5	
Other	1136	7.0	48	4.1	
SOT transplant type					<.001
Heart	1120	6.7	101	8.4	
Lung	1048	6.3	238	19.7	
Intestine	61	.37	22	1.8	
Liver	4348	26.3	380	31.5	
Kidney	8605	51.9	327	27.1	
Pancreas	601	3.6	52	4.3	
Heart and lung	30	.18	8	.66	
Kidney and pancreas	713	4.3	79	6.6	

SOT, solid organ transplantation.

Transplant patients who identified as Black had a lower odds of developing IFI when compared to patients who identified as White (OR .83, 95% CI .70–.98), while there was a protective association for people who identified as other (OR .53, 95% CI .40–.72). When adjusted for age, sex and transplant type, the association for Black patients was non-significant (OR=.97, 95% CI .82–1.15); however, the association for other remained significant (OR=.56, 95% CI .41–.75) (Table 2).

We evaluated specific mycoses in a multivariable model that included demographics and transplant type. Of those with aspergillosis there was a higher frequency of lung transplant patients compared to other organ transplant types (47%; $P<.0001$), of those with candidiasis there was a higher frequency of liver transplants compared to other organ transplant types (40%; $P<.0001$) and of those with cryptococcosis there was a higher frequency of kidney transplants compared to other organ transplant types (51.5%); $P<.0001$) (data not shown). Patients who identified as Black (OR=.55, 95% CI .34–.89) or other (OR=.29, 95% CI .34–89) compared to White patients had lower odds of invasive aspergillosis (Table 3). For invasive candidiasis there was no significant association for Black patients (OR=.98, 95% CI .78–1.23), but there was a protective association for patients who identified as other (OR=.67, 95% CI .46–0.97). Finally, when evaluating patients with cryptococcosis, Black patients (when compared to White patients) were at increased odds of developing infection (OR=2.19, 95% CI 1.35–3.54). People who identified as other had a reduced,

Table 2. Adjusted association of race and invasive fungal infection[a]

	OR	95% CI	*P*
Black	.97	.82–1.15	.71
Other	.56	.41–.75	<.001
Male	1.07	.95–1.20	.30
Age	1.11	1.06–1.16	<.001

[a] Model included transplant type, in addition to above variables.

Table 3. Adjusted association between race and specific IFIs[a]

	OR	95% CI	*P*
Aspergillosis			
Black	.55	.34–.89	.015
Other	.29	.12–.71	.006
Male	1.13	.86–1.48	.372
Age	1.29	1.17–1.43	<.001
Candidiasis			
Black	.98	.78–1.23	.842
Other	.67	.46–.97	.034
Male	1.18	1.00–1.39	.043
Age	.99	.95–1.05	.939
Cryptococcosis			
Black	2.19	1.35–3.54	.002
Other	.71	.26–1.95	.503
Male	.87	.57–1.33	.525
Age	1.52	1.28–1.80	<.001

IFI, invasive fungal infection.
[a] Models included transplant type, in addition to above variables.

but non-significant odds of cryptococcosis (OR=.71, 95% CI .26–1.95).

DISCUSSION

Our study investigated the association between race and IFI in a large, prospective US cohort of solid organ transplant patients. While previous studies have adjusted for race in the analysis of predictors for IFIs, assessing race as a main risk factor for IFI development in transplant recipients has been understudied.

Previous studies have illustrated that pharmacogenetic profiles of minorities may contribute to the incidence of acute transplant rejection, steroid resistance, and increased need for immunosuppressive drugs.[4] Despite potential pharmacogenetic differences, we observed no difference in the overall odds of developing an IFI between Blacks and Whites. However, other race was associated with a significant reduction in the odds of IFI.

When looking at specific types of mycoses, there were several differences between the racial groups. For invasive aspergillosis, Blacks or other racial

Despite potential pharmacogenetic differences, we observed no difference in the overall odds of developing an IFI between Blacks and Whites.

categories, when compared to Whites, had a significantly lower odds of infection in the adjusted model. Although White race has been associated with decreased risk of death among patients with invasive aspergillosis, the association of race and aspergillosis was unexpected and is difficult to explain.[15]

We observed that Black patients were approximately twice as likely to develop cryptococcosis when compared to White patients or patients of other racial categories. This observation suggests that there may be differences in innate genetic susceptibility or pharmacogenetic differences among races that could have an impact with this particular fungal infection. A similar increased risk of infection has been described in Blacks with symptomatic and disseminated coccidioidomycosis.[16,17] Additionally, there could be environmental exposures that could contribute to an increased risk of developing an invasive fungal infection that needs to be explored through further research.

An important limitation of our study is the lack of detailed information on race within the control dataset. This limits the variables we are able to compare between cases and controls that could contribute to invasive fungal infections including, but not limited to, diabetes, body mass index and level of immunosuppression. The race information in the case data included information on people who identify as White, Black, Asian/Pacific Islander, American Indian/Alaska Native and other; whereas, the control dataset listed people as White, Black and other. This limits the analysis to three racial groups, preventing us from investigating whether the protective effect is due to specific racial subgroups or ethnicity. In addition, due to a limited number of variables available in the control data set, our model could only contain demographic variables and transplant type. It is possible that unmeasured confounders, such as transplant immunosuppression, environmental factors or preventative measures may have impacted our results.

In conclusion, these observations from a large US dataset of SOT recipients suggest that Black patients are at no greater risk of developing IFI overall when compared to White patients, but they may be at a greater risk for cryptococcosis. Further research is needed to assess whether a genetic component, potentially increased immunosuppression or other factors may predispose Blacks to cryptococcal infection. The overall protective effect of the other group may be due to a genetic predisposition among Asians /Pacific Islanders, American Indian/Alaska Natives or other groups and warrants additional studies.

ACKNOWLEDGMENTS

TRANSNET was sponsored by the CDC, Astellas, Pfizer, Merck, and Schering Plough. We would like to thank the following TRANSNET Investigators: Barbara Alexander, MD, Duke University; Elias Anaissie, MD, University of Arkansas; Michael Boeckh, MD, Fred Hutchinson Cancer Research Center; Janice Brown, MD, Stanford University; Lisa Brumble, MD, Mayo Clinic-Jacksonville; Alison Freifeld, MD, University of Nebraska; Yoav Golan, MD, and Susan Hadley, MD, Tufts University; Loreen Herwaldt, MD, University of Iowa; James Ito, MD, City of Hope National Medical Center; Carol Kauffman, MD, University of Michigan; Katherine Knapp, MD, St. Jude Children's Hospital; Dimitrios Kontoyiannis, MD, MD Anderson Cancer Center; Kieren Marr, MD and Trish Perl, MD, Johns Hopkins Medical Institute; Vicki Morrison, MD, University of Minnesota; Genovefa Papanicolaou, MD, Memorial Sloan-Kettering Cancer Center; Tom Patterson, MD, University of Texas HSC-San

Antonio; Mindy Schuster, MD, University of Pennsylvania; Randall Walker, MD, Mayo Clinic-Rochester; Tom Walsh, MD, Weill Cornell Medical College; John Wingard, MD, University of Florida.

The findings and conclusions in this article are those of the authors and do not necessarily represent the views of the Centers of Disease Control and Prevention.

REFERENCES

1. Asrani SK, Kim WR, Kamath PS. Race and receipt of liver transplantation: Location matters. *Liver Transpl*. 2010;16:1009–1012.
2. Fan PY, Ashby VB, Fuller DS, et al. Access and outcomes among minority transplant patients, 1999–2008, with a focus on determinants of kidney graft survival. *Am J Transplant*. 2010;10:1090–1107.
3. Girnita DM, Webber SA, Ferrell R, et al. Disparate distribution of 16 candidate single nucleotide polymorphisms among racial and ethnic groups of pediatric heart transplant patients. *Transplantation*. 2006;82:1774–1780.
4. Higgins RS, Fishman JA. Disparities in solid organ transplantation for ethnic minorities: Facts and solutions. *Am J Transplant*. 2006;6:2556–2562.
5. Mathur AK, Schaubel DE, Gong Q, Guidinger MK, Merion RM. Racial and ethnic disparities in access to liver transplantation. *Liver Transpl*. 2010;16:1033–1040.
6. Churak JM. Racial and ethnic disparities in renal transplantation. *J Natl Med Assoc*. 2005;97:153–160.
7. Wolfe WA, Toomey E. An evolving strategy to increase the number of minority and low-income patients referred for transplantation. *Nephrol News Issues*. 2004;18:52:54–56.
8. Klein AS, Messersmith EE, Ratner LE, Kochik R, Baliga PK, Ojo AO. Organ donation and utilization in the united states, 1999–2008. *Am J Transplant*. 2010;10:973–986.
9. Kemmer NM, Neff GW. Liver transplantation trends and survival in the Asian population. *Transplantation*. 2009;88:392–394.
10. Fishman JA, Issa NC. Infection in organ transplantation: Risk factors and evolving patterns of infection. *Infect Dis Clin North Am*. 2010;24:273–283.
11. Pelletier SJ, Isaacs RB, Raymond DP, et al. Ethnic disparities in outcome from posttransplant infections. *Shock*. 2004;22:197–203.
12. Kontoyiannis DP, Marr KA, Park BJ, et al. Prospective surveillance for invasive fungal infections in hematopoietic stem cell transplant recipients, 2001–2006: overview of the transplant-associated infection surveillance network (TRANSNET) database. *Clin Infect Dis*. 2010;50:1091–1100.
13. Pappas PG, Alexander BD, Andes DR, et al. Invasive fungal infections among organ transplant recipients: results of the transplant-associated infection surveillance network (TRANSNET). *Clin Infect Dis*. 2010;50:1101–1111.
14. Hamurcu Z, Demirtas H, Ascioglu O, Donmez-Altuntas H, Aktas E. Micronucleus evaluation in mitogen-stimulated lymphocytes of puva treated patients. *Tohoku J Exp Med*. 2002;198:11–21.
15. Baddley JW, Andes DR, Marr KA, et al. Factors associated with mortality in transplant patients with invasive aspergillosis. *Clin Infect Dis*. 2010;50:1559–1567.
16. Woods CW, McRill C, Plikaytis BD, et al. Coccidioidomycosis in human immunodeficiency virus-infected persons in Arizona, 1994–1997: Incidence, risk factors, and prevention. *J Infect Dis*. 2000;181:1428–1434.
17. Rosenstein NE, Emery KW, Werner SB, et al. Risk factors for severe pulmonary and disseminated coccidioidomycosis: Kern county, California, 1995–1996. *Clin Infect Dis*. 2001;32:708–715.

AUTHOR CONTRIBUTIONS

Study design and concept: Andes, Chiller, Pappas, Baddley
Acquisition of data: Andes, Pappas
Data analysis and interpretation: Boehme, McGwin, Lyon, Baddley
Manuscript draft: Boehme, McGwin, Andes, Lyon, Chiller, Baddley
Statistical expertise: Boehme, McGwin, Baddley
Acquisition of funding: Pappas
Administrative: Lyon, Pappas, Baddley
Supervision: McGwin, Chiller, Baddley