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MAJOR ARTICLE

Racial Differences in Clinical Phenotype and Hospitalization of Blastomycosis Patients

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Background. Dimorphic fungal infections, such as blastomycosis, cause significant morbidity and mortality. Historically, blastomycosis studies have focused on non-Hispanic whites, which limits our understanding of the clinical presentation and outcomes for patients of other races and ethnicities. We evaluated whether clinical presentation and disease severity varied across racial and ethnic groups.

Methods. Blastomycosis patients were identified from Marshfield Clinic Health System and data were abstracted from electronic medical records. *Blastomyces* genotyping was performed for cases with available isolates. Bivariate analyses (χ^2 tests/analysis of variance) assessed associations of race and/or ethnicity, *Blastomyces* spp, and hospitalization status with demographics and clinical presentation. Multivariable logistic regression was used to evaluate the association of race and/or ethnicity and hospitalization.

Results. In total, 477 patients were included. Age differences were observed across race and ethnicity categories ($P < .0001$). Non-Hispanic whites were oldest (median, 48 years; interquartile range [IQR], 31–62) and Asians were youngest (26 years; IQR, 19–41). Non-Hispanic whites (55%) and African Americans (52%) had underlying medical conditions more frequently than Hispanic whites (27%) and Asians (29%). Odds of hospitalization were 2 to 3 times higher for Hispanic whites (adjusted odds ratio [aOR], 2.9; 95% confidence interval [CI], 1.2–1.7), American Indian or Alaska Native (AIAN) (aOR, 2.4; 95% CI, 1.0–5.5), and Asian (aOR, 1.9; 95% CI, 1.0–3.6) patients compared with non-Hispanic white patients. Ninety percent of *Blastomyces dermatitidis* infections occurred in non-Hispanic whites, whereas blastomycosis in Hispanic whites, AIAN, and Asian patients was frequently caused by *Blastomyces gilchristii* ($P < .0001$).

Conclusions. Hispanic whites, AIAN, and Asian blastomycosis patients were younger and healthier but more frequently hospitalized. Patients in these racial and ethnic groups may need more aggressive treatment and closer therapeutic monitoring.

Keywords: *Blastomyces*; blastomycosis; ethnicity; hospitalization; race.

Dimorphic fungal infections, including blastomycosis, histoplasmosis, coccidioidomycosis, and paracoccidioidomycosis, are the most common cause of invasive fungal disease worldwide causing several million infections annually [1, 2]. Incidence of fungal infections is increasing [3], and, unlike opportunistic fungi, dimorphic fungi infect both immunocompromised and immunocompetent individuals. Dimorphic fungi have the unique ability to change morphology in response to environmental conditions [4]. The fungi convert from nonpathogenic mold in the soil to pathogenic yeast after infectious spores are inhaled into the lungs of humans or other mammalian hosts. Morphologic conversion of the fungi from mold to yeast provides downregulation of the host immune system [5] and is required for virulence [2]. However, the virulence mechanisms of dimorphic fungal infections are just beginning to be explored [6–8].

Blastomyces spp, the etiological agent of blastomycosis, is endemic to the Great Lakes region and Mississippi River Valley [9]. The organism poses a significant public health threat and has been associated with numerous outbreaks in Wisconsin, USA [10–13]. Clinical manifestations are primarily pulmonary, but dissemination to other tissues is common [14, 15]. In many cases, it is difficult to determine which patients will have disseminated disease, severe respiratory failure, or death, making individualized treatment challenging. In recent studies, the cellular mechanisms of *Blastomyces* infection [16, 17] and the association between organism genotype and dissemination of infection have been described [15], making *Blastomyces* an ideal model organism for studying dimorphic fungal disease.

Six distinct species of *Blastomyces* have been described [18–20] with 4 being pathogenic to humans, although identifying *Blastomyces* to the species level is not routinely performed

Received 11 July 2019; editorial decision 27 September 2019; accepted 1 October 2019.

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Open Forum Infectious Diseases®

DOI: 10.1093/ofid/ofz438

in a clinical diagnostic setting. *Blastomyces percursus* and *Blastomyces helicus* have only recently been recategorized based on genetic sequencing; therefore, not much is known regarding the clinical phenotype in humans. In contrast, the other 2 species infecting humans have been studied extensively, with *Blastomyces gilchristii* being more often associated with pulmonary-only disease and *Blastomyces dermatitidis* being more likely to disseminate [15].

Currently, clinical descriptions and treatment guidelines for blastomycosis are based largely on studies of the disease in white patients, which dominate the literature. Despite this, some studies have reported clinical differences among racially diverse blastomycosis patients. In one Wisconsin, USA study, white patient's clinical isolates were more often *B dermatitidis* compared with patients of other races [15]. Other studies have shown that the incidence of blastomycosis infection, disseminated disease, and mortality are higher in black patients compared with white patients [21–24]. Higher incidence of blastomycosis has also been observed in aboriginal populations in Canada [25], American Indians [26], and Asians [13, 21] compared with whites. *Coccidioides* spp, a related dimorphic fungi, has been shown to cause disseminated disease more frequently in Asians (especially Pacific Islanders and Filipinos), Hispanics, and blacks [27, 28]. These studies, taken together, suggest that significant differences may exist in the clinical phenotype of dimorphic fungal diseases, including blastomycosis, in patients of varying racial/ethnic backgrounds. We hypothesize that patient racial and ethnic background is significantly associated with clinical differences in blastomycosis patients in Wisconsin. In this retrospective study of Wisconsin cases, we report the patient demographics, underlying medical conditions (UMCs), clinical disease features, and hospitalization of a large cohort of blastomycosis patients, by race and etiologic *Blastomyces* spp.

METHODS

Study Participants

This study was conducted at Marshfield Clinic Health System (MCHS), located in central and northern Wisconsin in an area endemic for blastomycosis. Marshfield Clinic Health System comprises 62 clinics and medical offices, 6 hospitals and Marshfield Labs, which serves as a clinical reference laboratory for the region. We identified cases within past data sets and performed a data query of MCHS electronic medical records to identify additional blastomycosis cases, using *International Classification of Diseases, Ninth Revision* (ICD9) and *Tenth Revision* (ICD10), from 1999 through early 2016.

Case inclusion criteria were as follows: (1) laboratory confirmation of blastomycosis using standard culture methods or visualization of the yeast on cytology or histopathology; (2) clinical data were available from either a previous data set or MCHS electronic medical record; and (3) patients identified themselves as being of a single race including white, black or African American (AA), Asian, and American Indian or Alaska Native (AIAN). Hispanic ethnicity data was collected on all white patients.

Patients diagnosed with blastomycosis only by *Blastomyces* antigen or antibody testing were excluded from this study. All aspects of the study were reviewed and approved by the institutional review board of the MCHS.

Data Abstraction

Clinical data were abstracted as previously described [15] from each medical record. A total of 36 data elements were collected for each case. Patient demographics included the following: age at diagnosis, gender, race/ethnicity, and smoking status. Race/ethnicity was categorized as non-Hispanic white, AIAN, Asian, Hispanic white, and AA. Underlying medical condition's were categorized as follows: circulatory (coronary artery disease, congestive heart failure, hypertension, and hypercholesterolemia/hyperlipidemia), endocrine (diabetes and hypothyroidism), immune suppression (cancer and human immunodeficiency virus/acquired immune deficiency syndrome), and pulmonary (emphysema, chronic obstructive pulmonary disease, and asthma). Clinical disease characteristics included the following: symptoms (cough, hemoptysis, fever, chills, sweats, poor appetite, weight loss, joint pain, back pain, muscle pain, chest pain, bone pain, fractures, headache, and fatigue), hospitalization status, and mortality. All antifungal drug(s) used during the course of treatment were abstracted for each patient. Location of each patient's infection was categorized as pulmonary-only if the patient had no evidence of disease outside the lungs and disseminated if they had evidence of infection anywhere outside of or in addition to the lungs. The time from disease onset (patient reported symptom onset, documented in medical record) to diagnosis (date of first positive fungal culture or visualization of the yeast by cytology or histopathology) was determined for each patient and categorized as >1 month or ≤1 month.

Blastomyces Species Genotyping

Blastomyces spp genotyping was performed for cases with a clinical isolate available. *Blastomyces* isolates were not available for cases if the initial laboratory diagnosis was made outside of MCHS. Deoxyribonucleic acid from each cultured isolate was extracted as previously described [15]. Species typing of each isolate was performed by either Sanger sequencing or single-nucleotide polymorphism analysis [29] of the internal transcribed spacer 2 (*its2*). Species assignment was based on a fixed nucleotide difference between *B dermatitidis* and *B gilchristii* at position 19 [18].

Statistical Analysis

Patient demographic, clinical, and treatment characteristics were summarized and compared in the full dataset across race categories and hospitalization status. In the subset for which

species was known, characteristics were also summarized by *Blastomyces* spp, Pearson χ^2 tests (Fisher's exact test for small sample sizes) were used for categorical variables, and Kruskal-Wallis analysis of variance (ANOVA) or 2-sample *t* tests were used for continuous variables. Bonferroni-adjusted *P* values were calculated for all comparisons (shown in tables).

To describe differences in characteristics between specific race groups, post hoc tests for categorical variables were performed using log-binomial regression in Proc Glimmix, and post hoc tests for continuous variables were performed using ANOVA, both with Bonferroni multiple comparison adjustment. *P* values for these post hoc tests are reported in the text when appropriate to support statements of difference.

Multivariable logistic regression modeling was conducted to assess the association between race and hospitalization, as a measure of severity of disease, for blastomycosis infection in the complete dataset. Race was treated as a 5-level variable with non-Hispanic whites as the referent group. We controlled for age, gender, presence of UMC, smoking status, and pulmonary-only infection because these have been suggested as related to hospitalization or death in prior studies of blastomycosis [15, 30]. All analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC).

RESULTS

Study Participants and Descriptive Data

Two hundred twenty-seven cases from previous data sets met the inclusion criteria for this study [15]. An additional 390 cases were identified within MCHS electronic medical records; of those, 140 were removed for the following reasons: diagnosis could not be confirmed (n = 16), patient race or ethnicity was unknown (n = 122), or the patient identified as biracial (n = 2). A total of 477 cases of blastomycosis were included in this study.

Patients identified themselves by the following racial groups: non-Hispanic white (n = 302, 63%), Hispanic white (n = 34, 7%), AA (n = 27, 6%), Asian (n = 76, 16%), and AIAN (n = 38, 8%). The age of patients at diagnosis ranged from 2 to 97 years (median, 42.0; interquartile range [IQR], 25–55) and 313 (66%) were male. Underlying medical conditions were identified in 228 patients (48%). Disseminated disease was observed in 97 (20%) cases, with 12 patients (3%) having multiple sites of dissemination. The majority of patients were diagnosed with blastomycosis ≤1 month from the onset of their symptoms (n = 334, 70%) and were hospitalized (n = 296, 63%) during the course of their disease. Most patients were treated with itraconazole (n = 402, 88%) at some point in their illness. Thirty-one cases (7%) resulted in death.

Characteristics by Race or Ethnicity

Results of analyses across all racial and ethnic groups are presented in Table 1. Hispanic whites (31 years; IQR, 24–43), AIAN (28 years; IQR, 18–40), and Asians (26 years; IQR, 19–41) were significantly younger than non-Hispanic white (48 years; IQR, 31–62) (adjusted *P* = .0003 for each comparison to non-Hispanic white). In post hoc analyses, Asians were less likely to be current smokers than AIAN (42%, *P* = .0056), AA (38%, *P* = .0246), and non-Hispanic whites (33%, *P* = .0128). Asian patients were significantly less likely to have a UMC(s) than non-Hispanic white patients (*P* = .0049). Fatigue and muscle pain were clinical symptoms that varied significantly across the racial groups (Table 1). Amphotericin B treatment was less common in patients who identified as non-Hispanic white compared with AIAN (*P* = .0404) and Asian patients (*P* = .0001), in post hoc analyses. Across all racial and ethnic groups, more than half of case patients experienced hospitalization, with Hispanic whites (76%), AIAN (76%), and Asians the highest (72%). Hospitalization was significantly higher in Asian patients compared with non-Hispanic whites (*P* = .0382).

Race or Ethnicity and *Blastomyces* Species

The percentage of infections caused by *B gilchristii* and *B dermatitidis* was significantly different across racial and/or ethnic groups (*P* = .0035) (Table 1). Clinical isolates of *Blastomyces* were available for genotyping on 284 cases in the study. *Blastomyces gilchristii* was the etiologic agent in 172 (61%) blastomycosis cases, and *B dermatitidis* was the etiologic agent in 112 (39%) blastomycosis cases (Table 2). Ninety percent of cases caused by *B dermatitidis* occurred in non-Hispanic white patients. Alternatively, only 73% of cases caused by *B gilchristii* occurred in non-Hispanic white patients. Cases in AIAN and Asians made up 9% and 13% of *B gilchristii* cases, respectively.

Characteristics by *Blastomyces* Species

Association analysis correlating clinical features of disease with *Blastomyces* spp revealed that infections caused by *B gilchristii* were more likely to be associated with pulmonary-only infections (91% vs 66%, *P* = .0035), and patients were more likely to report fever (77% vs 53%, *P* = .0035 than with *B dermatitidis* (Table 2). In contrast, patients infected with *B dermatitidis* were more likely to have UMC(s) (62% vs 36%, *P* = .0035), be current smokers (49% vs 23%, *P* = .0035), and be older (53 years, standard deviation [SD] = 19 vs 35 years, SD = 20; *P* = .0035) than patients with *B gilchristii*.

Characteristics by Hospitalization

Hospitalization status was available for 470 cases (Table 3). Fever (78% vs 50%, *P* = .0034) was reported more frequently among hospitalized cases than nonhospitalized cases. Hospitalized patients were more likely to receive amphotericin B treatment (35% vs 1%, *P* = .0034) than nonhospitalized patients, whereas nonhospitalized patients were more likely to receive itraconazole (95% vs 84%, *P* = .0136). We were surprised to find that hospitalized

Table 1. Patient Demographic, Clinical and Treatment Characteristics for 477 Human Blastomycosis Cases by Race/Ethnicity[a]

Demographic/Condition	Total n = 477	Non-Hispanic Whiten = 302	Hispanic Whiten = 34	American Indian/ Alaskan Native n = 38	Asiann = 76	Black/African American n = 27	*P* Value[b]	Adjusted *P* Value[c]
Age at diagnosis, median (IQR)	42 (25–55)	48 (31–62)	31 (24–43)	28 (18–40)	26 (19–41)	44 (27–53)	<.0001	.0035
Female	164 (34)	101 (33)	8 (24)	20 (53)	26 (34)	9 (33)	.1110	1.000
Current smoker	143 (31)	98 (33)	10 (31)	15 (42)	10 (13)	10 (38)	.0068	.2380
UMC(s)	228 (48)	165 (55)	9 (27)	18 (47)	22 (29)	14 (52)	.0002	.0070
Circulatory[d]	131 (27)	99 (33)	4 (12)	8 (21)	16 (21)	4 (15)	.0129	.4515
Endocrine[e]	107 (22)	68 (23)	3 (9)	14 (37)	14 (18)	8 (30)	.0510	1.000
Immune suppression[f]	22 (5)	20 (7)	1 (3)	0 (0)	0 (0)	1 (4)	.0539	1.000
Pulmonary[g]	51 (11)	43 (14)	1 (3)	3 (8)	2 (3)	2 (7)	.0140	.4900
Blastomyces spp							<.0001	.0035
B gilchristii	172 (36)	126 (42)	6 (18)	16 (42)	23 (30)	1 (4)		
B dermatitidis	112 (23)	101 (33)	3 (9)	3 (8)	2 (3)	3 (11)		
Unknown	193 (41)	75 (25)	25 (74)	19 (50)	51 (67)	23 (85)		
Clinical Symptoms								
Back pain	96 (21)	53 (18)	11 (32)	9 (25)	14 (19)	9 (33)	.1442	1.000
Bone pain	56 (12)	41 (14)	4 (12)	4 (11)	4 (5)	3 (11)	.3421	1.000
Chest pain	241 (52)	148 (50)	19 (56)	18 (49)	42 (57)	14 (52)	.8426	1.000
Chills	232 (50)	143 (48)	19 (56)	11 (31)	46 (61)	13 (48)	.0485	1.000
Cough	413 (87)	256 (86)	32 (94)	31 (82)	72 (95)	22 (81)	.0787	1.000
Deep tissue abscess	13 (3)	7 (2)	0 (0)	1 (3)	4 (5)	1 (4)	.4567	1.000
Fatigue	309 (67)	211 (72)	24 (71)	13 (37)	44 (59)	17 (63)	.0005	.0175
Fever	310 (66)	181 (61)	25 (74)	23 (62)	64 (85)	17 (63)	.0017	.0595
Fractures	8 (2)	5 (2)	0 (0)	2 (5)	1 (1)	0 (0)	.4603	1.000
Headache	129 (28)	86 (30)	12 (35)	6 (17)	19 (26)	6 (22)	.4143	1.000
Hemoptysis	83 (18)	41 (14)	9 (26)	9 (24)	19 (26)	5 (19)	.0530	1.000
Joint pain	105 (23)	74 (26)	11 (32)	6 (17)	7 (9)	7 (26)	.0231	.8085
Muscle pain	139 (30)	106 (37)	10 (29)	4 (11)	10 (14)	9 (33)	.0002	.0070
Night sweats	214 (46)	138 (47)	19 (56)	11 (30)	34 (45)	12 (44)	.2467	1.000
Poor appetite	234 (51)	152 (52)	21 (62)	12 (33)	37 (50)	12 (44)	.1552	1.000
Skin lesions	69 (15)	52 (17)	4 (12)	4 (11)	5 (7)	4 (15)	.1842	1.000
Weight loss	214 (46)	137 (46)	24 (71)	14 (38)	25 (34)	14 (52)	.0069	.2415
Pulmonary-only	380 (80)	238 (79)	28 (82)	30 (79)	66 (87)	18 (67)	.2441	1.000
Treatment[h]								
Fluconazole	34 (8)	26 (9)	2 (7)	3 (9)	2 (3)	1 (5)	.4741	1.000
Itraconazole	402 (88)	262 (89)	28 (93)	27 (79)	67 (91)	18 (86)	.4364	1.000
Ketoconazole	5 (1)	2 (0.7)	1 (3)	1 (3)	1 (1)	0 (0)	.2548	1.000
Voriconazole	14 (3)	5 (2)	1 (3)	3 (9)	5 (7)	0 (0)	.0323	1.000
Amphotericin B	100 (22)	48 (16)	9 (30)	12 (34)	28 (38)	3 (14)	.0002	.0070
Onset to diagnosis >1 month	143 (30)	98 (32)	13 (38)	8 (21)	14 (18)	10 (37)	.0712	1.000
Hospitalization	296 (63)	172 (58)	25 (76)	29 (76)	53 (72)	17 (65)	.0219	.7665
Death from blastomycosis	31 (7)	23 (8)	2 (6)	2 (5)	3 (4)	1 (4)	.8601	1.000

Abbreviations: IQR, interquartile range; UMCs, underlying medical conditions.

[a]Data are presented as number (column %) except were indicated.

[b]*P* values for categorical variables were calculated with χ^2 test (Fisher's exact for small sample sizes); *P* values for continuous variables were calculated with Kruskal-Wallis analysis of variance.

[c]*P* values were adjusted with Bonferroni correction.

[d]Includes coronary artery disease, congestive heart failure, hypertension, and hypercholesterolemia/hyperlipidemia.

[e]Includes diabetes and hypothyroidism.

[f]Includes cancer and human immunodeficiency virus/acquired immune deficiency syndrome.

[g]Includes asthma, chronic obstructive pulmonary disease, emphysema.

[h]Includes all antifungal drugs prescribed during the course of treatment; patients may have had more than 1 antifungal drug.

patients were diagnosed faster, with only 23% being diagnosed >1 month after symptom onset compared with 43% for nonhospitalized patients ($P = .0034$), but they were more likely to die from their infection (10% vs 1%, $P = .0102$) than nonhospitalized patients.

Results of Hospitalization Multivariable Analyses

The association of race and ethnicity to hospitalization was significant in the unadjusted ($P = .02$) and adjusted models ($P = .03$) (Table 4). Hispanic whites (odds ratio [OR], 2.5; 95% confidence interval [CI], 1.1–6.0), AIAN (OR, 2.2; 95% CI, 1.0–4.8), and

Table 2. Patient Demographic, Clinical and Treatment Characteristics by *Blastomyces* spp for 284 Human Blastomycosis Cases[a]

Demographic/Condition	Total n = 284	*Blastomyces dermatitidis* n = 112	*Blastomyces gilchristii* n = 172	*P* Value[b]	Adjusted *P* Value[c]
Age at diagnosis, mean (SD)	42 (22)	53 (19)	35 (20)	<.0001	.0035
Female	100 (35)	36 (32)	64 (37)	.3823	1.0000
Race				.0001	.0035
Non-Hispanic White	227 (80)	101 (90)	126 (73)		
Hispanic White	9 (3)	3 (3)	6 (3)		
American Indian/Alaskan Native	19 (7)	3 (3)	16 (9)		
Asian	25 (9)	2 (2)	23 (13)		
Black/African American	4 (1)	3 (3)	1 (1)		
Current smoker	92 (33)	54 (49)	38 (23)	<.0001	.0035
UMC(s)	130 (46)	69 (62)	61 (36)	<.0001	.0035
Circulatory[d]	73 (26)	42 (38)	31 (18)	.0002	.0070
Endocrine[e]	54 (19)	25 (22)	29 (17)	.2517	1.0000
Immune Suppression[f]	14 (5)	10 (9)	4 (2)	.0120	.4200
Pulmonary[g]	33 (12)	17 (15)	16 (9)	.1310	1.0000
Clinical Symptoms					
Back pain	64 (23)	25 (24)	39 (23)	.9649	1.0000
Bone pain	44 (16)	21 (20)	23 (14)	.1979	1.0000
Chest pain	152 (54)	51 (46)	101 (60)	.0200	.7000
Chills	146 (52)	50 (45)	96 (56)	.0609	1.0000
Cough	249 (88)	90 (81)	159 (92)	.0041	.1435
Deep tissue abscess	6 (2)	2 (2)	4 (2)	1.0000	1.0000
Fatigue	199 (72)	71 (66)	128 (75)	.1263	1.0000
Fever	191 (67)	59 (53)	132 (77)	<.0001	.0035
Fractures	7 (2)	2 (2)	5 (3)	.7064	1.0000
Headache	91 (33)	29 (27)	62 (37)	.0921	1.0000
Hemoptysis	46 (16)	21 (19)	25 (15)	.3571	1.0000
Joint pain	75 (27)	33 (31)	42 (25)	.2890	1.0000
Muscle pain	88 (32)	30 (29)	58 (35)	.3060	1.0000
Night sweats	136 (49)	45 (41)	91 (54)	.0408	1.0000
Poor appetite	146 (53)	52 (48)	94 (56)	.2049	1.0000
Skin lesions	43 (15)	29 (26)	14 (8)	<.0001	.0035
Weight loss	131 (47)	54 (49)	77 (45)	.5340	1.0000
Pulmonary-only	228 (81)	73 (66)	155 (91)	<.0001	.0035
Treatment[h]					
Fluconazole	22 (8)	6 (6)	16 (10)	.2113	1.0000
Itraconazole	240 (87)	90 (82)	150 (90)	.0391	1.0000
Ketoconazole	3 (1)	2 (2)	1 (1)	.5651	1.0000
Voriconazole	10 (4)	2 (2)	8 (5)	.3243	1.0000
Amphotericin B	59 (21)	22 (20)	37 (22)	.6774	1.0000
Onset to diagnosis >1 month	78 (28)	48 (43)	30 (17)	<.0001	.0035
Hospitalization	176 (62)	60 (54)	116 (68)	.0155	.5425
Death from Blastomycosis	23 (8)	13 (12)	10 (6)	.0709	1.0000

Abbreviations: SD, standard deviation; UMCs, underlying medical conditions.

[a]Data are presented as number (column %) except were indicated.

[b]*P* values for categorical variables were calculated with χ^2 test; *P* values for continuous variables were calculated with *t* tests.

[c]*P* values were adjusted with Bonferroni correction.

[d]Includes coronary artery disease, congestive heart failure, hypertension, and hypercholesterolemia/hyperlipidemia.

[e]Includes diabetes and hypothyroidism.

[f]Includes cancer and human immunodeficiency virus/acquired immune deficiency syndrome.

[g]Includes asthma, chronic obstructive pulmonary disease, and emphysema.

[h]Includes all antifungal drugs prescribed during the course of treatment; patients may have had more than 1 antifungal drug.

Asians (OR, 1.9; 95% CI, 1.1–3.4) had approximately 2 times higher odds of hospitalization compared with non-Hispanic whites in the unadjusted model. The adjusted OR (aOR) for Hispanic whites and AIAN increased slightly to 2.9 (95% CI, 1.2–7.1) and 2.4 (95% CI, 1.0–5.5), respectively, whereas the aOR for Asians remained the same at 1.9 (95% CI, 1.0–3.6).

Table 3. Patient Demographic, Clinical and Treatment Characteristics by Hospitalization Status for 470 Human Blastomycosis Cases[a]

Demographic/Condition	Total n = 470	Non-Hospitalized n = 174	Hospitalized n = 296	*P* Value[b]	Adjusted *P* Value[c]
Age at diagnosis, mean (SD)	42 (20.0)	43 (18.7)	41 (20.8)	.4421	1.0000
Female	161 (34)	55 (32)	106 (36)	.3540	1.0000
Race/Ethnicity				.0219	.7446
Non-Hispanic White	299 (63)	127 (73)	172 (58)		
Hispanic White	33 (7)	8 (5)	25 (8)		
American Indian/Alaskan Native	38 (8)	9 (5)	29 (10)		
Asian	74 (16)	21 (12)	53 (18)		
Black/African American	26 (6)	9 (5)	17 (6)		
Current smoker	140 (31)	60 (35)	80 (28)	.0872	1.0000
UMC(s)	226 (48)	74 (43)	152 (52)	.0674	1.0000
Circulatory[d]	131 (28)	45 (26)	86 (29)	.4429	1.0000
Endocrine[e]	107 (23)	30 (17)	77 (26)	.0272	.9248
Immune Suppression[f]	22 (5)	8 (5)	14 (5)	.9416	1.0000
Pulmonary[g]	50 (11)	14 (8)	36 (12)	.1587	1.0000
Clinical Symptoms					
Back pain	95 (21)	29 (17)	66 (23)	.1515	1.0000
Bone pain	56 (12)	20 (12)	36 (13)	.8341	1.0000
Chest pain	238 (51)	88 (52)	150 (51)	.9058	1.0000
Chills	229 (49)	69 (40)	160 (55)	.0023	.0782
Cough	408 (87)	146 (85)	262 (89)	.2575	1.0000
Deep tissue abscess	11 (2)	3 (2)	8 (3)	.7536	1.0000
Fatigue	307 (67)	106 (63)	201 (69)	.1799	1.0000
Fever	309 (66)	86 (50)	223 (78)	<.0001	.0034
Fractures	8 (2)	4 (2)	4 (1)	.4755	1.0000
Headache	128 (28)	49 (29)	79 (27)	.7027	1.0000
Hemoptysis	81 (17)	27 (16)	54 (18)	.4729	1.0000
Joint pain	104 (23)	36 (21)	68 (23)	.6326	1.0000
Muscle pain	136 (30)	56 (33)	80 (28)	.2026	1.0000
Night sweats	212 (46)	76 (45)	136 (46)	.7218	1.0000
Poor appetite	232 (50)	69 (41)	163 (56)	.0012	.0408
Skin lesions	68 (15)	41 (24)	27 (9)	<.0001	.0034
Weight loss	212 (46)	63 (37)	149 (51)	.0045	.1530
Pulmonary-only	378 (81)	126 (73)	252 (85)	.0017	.0578
Treatment[h]					
Fluconazole	34 (8)	7 (4)	27 (10)	.0392	1.0000
Itraconazole	395 (88)	158 (95)	237 (84)	.0004	.0136
Ketoconazole	5 (1)	2 (1)	3 (1)	1.0000	1.0000
Voriconazole	14 (3)	0 (0)	14 (5)	.0036	.1224
Amphotericin B	99 (22)	1 (1)	98 (35)	<.0001	.0034
Onset to diagnosis >1 month	138 (29)	72 (43)	66 (23)	<.0001	.0034
Death from blastomycosis	31 (7)	2 (1)	29 (10)	.0003	.0102

Abbreviations: SD, standard deviation; UMCs, underlying medical conditions.

[a]Data are presented as number (column %) except were indicated.

[b]*P* values for categorical variables were calculated with χ^2 test; *P* values for continuous variables were calculated with tests.

[c]*P* values were adjusted with Bonferroni correction.

[d]Includes coronary artery disease, congestive heart failure, hypertension, and hypercholesterolemia/hyperlipidemia.

[e]Includes diabetes and hypothyroidism.

[f]Includes cancer and human immunodeficiency virus/acquired immune deficiency syndrome.

[g]Includes asthma, chronic obstructive pulmonary disease, and emphysema.

[h]Includes all antifungal drugs prescribed during the course of treatment; patients may have had more than 1 antifungal drug.

DISCUSSION

We found that significant differences in clinical presentation and disease severity measures for blastomycosis infection are evident in patients from different racial and ethnic groups. Asian, AIAN, and Hispanic white patients were younger, with Asian patients being least likely to have a UMC(s), than non-Hispanic white patients. Despite this, Asian and AIAN patients were more likely to be treated with amphotericin B, and all 3 groups had 2–3 times higher odds of hospitalization. Although prior smaller studies have suggested that Asian and Aboriginal

Table 4. Unadjusted and Adjusted Logistic Regression Analysis Estimating Odds of Hospitalization Among Blastomycosis Cases by Race (Wisconsin, 1999–2016)

Characteristic	uOR (95% CI)	aOR (95% CI)[b]
Race/Ethnicity[a]		
Non-Hispanic White	REF	REF
Hispanic White	2.5 (1.1–6.0)	2.9 (1.2–7.1)
American Indian/Alaskan Native	2.2 (1.0–4.8)	2.4 (1.0–5.5)
Asian	1.9 (1.1–3.4)	1.9 (1.0–3.6)
Black/African American	1.3 (0.6–3.0)	1.5 (0.6–3.7)
Age at diagnosis		1.0 (1.0–1.0)
Female		1.1 (0.7–1.7)
Current smoker		0.8 (0.5–1.1)
Underlying medical condition(s)		1.9 (1.2–3.0)
Pulmonary-only		2.1 (1.3–3.4)

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; REF, reference; uOR, unadjusted odds ratio.

[a]Race was treated as a 5 level variable with non-Hispanic White as the referent group.

[b]Adjusted model controlled for age, gender, presence of underlying medical condition, smoking status, and pulmonary-only infection.

patients with blastomycosis are more likely to be younger, nonsmokers, and have fewer UMCs [13, 25], to our knowledge, this is the first large-scale study to demonstrate clinical differences and severity measures in blastomycosis patients across racial and ethnic groups.

Due to previously observed disparate rates of incidence, disseminated disease, and mortality from blastomycosis in specific racial and ethnic groups [13, 21–26], we chose a priori to investigate hospitalization as a severity measure in this study. Multivariable analysis revealed that after controlling for age, gender, UMC(s), smoking status, and pulmonary-only involvement, odds of hospitalization were approximately 2 to 3 times higher for Hispanic whites, AIAN, and Asian patients compared with non-Hispanic white patients. Amphotericin B treatment is administered to life-threatening cases within a hospital setting and varies significantly across racial and ethnic groups in our data. Although the bivariate association of hospitalization to racial and ethnic groups failed to meet $P < .05$ threshold of significance after Bonferroni adjustment, P values should not be strictly relied upon to judge clinical significance. The results of the multivariable model coupled with the significant variation of treatment with amphotericin B suggests that differences in severity by racial and/or ethnic groups should be further explored.

Exposure, strain virulence, and host immune factors likely play a role in variation in clinical presentation and outcomes in patients with blastomycosis of diverse racial or ethnic backgrounds. Exposure is generally difficult to define in blastomycosis cases because most people have multiple potential environmental exposures. In this study, we did not have access to data regarding residence, recreational activities, or employment so we were limited in exploring exposure as a variable. We previously demonstrated that patients with *B gilchristii* infection are more likely than those with *B dermatitidis* to have acute, pulmonary-only disease requiring hospitalization [15]. In this study, we found that patients who were Hispanic white, AIAN, or Asian were more likely to be infected with *B gilchristii* than other racial or ethnic groups. It is possible that Hispanic white, AIAN, and Asian patients are more frequently exposed to or differentially susceptible to this strain of *Blastomyces*. Susceptibility to fungal infections has been associated with variants in innate immune response genes. Toll-like receptor (TLR) 2 has been shown to play a key role in cellular recognition of *Coccidioides*, *Histoplasma*, and *Sporothrix* [31, 32], and polymorphisms in TLRs, Dectin-1, and DC-SIGN have been associated with susceptibility to candidemia and aspergillosis [33–35]. A recent study revealed that interleukin-6 may be an important blastomycosis susceptibility locus in the Hmong population [36]. It is highly likely that many of the additional genes mentioned above contain variants that differ between racial and/or ethnic groups and that they are important for susceptibility, recognition, and immune response to *Blastomyces* and other dimorphic fungal infections.

More important, clinicians in areas endemic for blastomycosis should maintain a high degree of suspicion for blastomycosis, particularly in Asian, AIAN, and Hispanic white patients because these patients likely present more acutely and have higher severity of disease necessitating more aggressive medical treatment. Because the symptoms of blastomycosis may mimic other respiratory illnesses, such as pneumonia, delays in diagnosis are common and may result in worse outcomes [37]. In addition, blastomycosis patients in some racial and ethnic groups may need closer therapeutic monitoring. Itraconazole is the primary drug for mild to moderate disease and is frequently prescribed as first-line therapy or for step-down therapy after amphotericin B. Azoles are metabolized by cytochrome P450 (P450) enzymes, in the liver. Asians have been shown to carry gene variants in several P450 regions, particularly CYP2C19 and CYP2D6, making them more likely to be poor metabolizers of drugs that involve those enzymes [38, 39]. Although we collected data on the prescribed and administered medications for treatment of blastomycosis infection, we did not determine whether medications and dosages were modified secondary to toxicity or treatment failure. It would not be evident in our data whether dosages had to be increased, or treatment time extended, due to subtherapeutic blood serum levels. Current Infectious Disease Society of America recommendations are that serum levels of itraconazole should be determined after 2 weeks of treatment to ensure adequate drug exposure, with a goal of a patient serum level of >1.0 but <10 μg/mL [36]. Despite these recommendations, we have anecdotally found that physicians at our institution monitor drug serum levels in approximately 50% of blastomycosis patients (Klaire Laux, 2019 unpublished data). It is unclear how often this recommendation is followed at other institutions.

We believe our study has numerous strengths. Access to a large cohort of racially diverse blastomycosis patients provided sufficient power to detect variation across most clinical features and disease outcomes. Detailed clinical data for these patients allowed for assessment of specific patient-level factors that have been limited in other epidemiologic studies. In addition, the inclusion of *Blastomyces* genotyping data permitted us to examine the impact of pathogen, in addition to race and ethnicity, on clinical features of this disease. However, this research is subject to several limitations. This study was retrospective in nature and relied on accuracy and completeness of electronic medical records. In addition, all patients included in this study were medically attended in Wisconsin, USA, and therefore this study does not represent the entire geographic or clinical range of blastomycosis. Finally, our analysis was limited by several factors. Given the novel and exploratory nature of this paper, we believed it was crucial to examine any and all potential relationships between variables. Bonferroni adjustments were applied to reduce the possibility of potentially false associations due to the number of calculations performed. This being said, Bonferroni adjustments can be extremely conservative and should be viewed with caution because associations that are real or clinically relevant may be discounted. We have provided both the raw *P* value and the Bonferroni corrected value for readers to interpret as they see fit. In addition, for some data fields including death, statistical power of this study was limited by small numbers of patients in some racial and ethnic groups. Interpretation of the subset analysis of cases with a clinical isolate was somewhat restricted because we were more likely to have a clinical isolate and determine *Blastomyces* spp on non-Hispanic white patients due to the demographics of our service area.

CONCLUSIONS

The data presented in this manuscript reveal significant racial and/or ethnic differences in clinical presentation and severity of infection of blastomycosis patients. To date, clinical descriptions of blastomycosis in the literature are based largely on studies of the disease in non-Hispanic white patients, which may not be representative of diverse patient populations. Our data shows that Hispanic white, AIAN, and Asian patients are presenting not only as younger and healthier, but with different symptomology and higher severity of illness compared with non-Hispanic white patients. It is possible that these patients may need more aggressive treatment and closer therapeutic monitoring. This study, along with previous work showing increased incidence of blastomycosis and severity of infection in some racial and ethnic populations, suggests that patient genetics likely influence host susceptibility and immune response to blastomycosis. Future studies examining host genetic features that contribute to the susceptibility and clinical disease characteristics of blastomycosis will be important in understanding these underlying differences. In addition, further investigation of patient P450 allele status and azole treatment could greatly benefit our knowledge and lead to better patient care and treatment of blastomycosis, along with other dimorphic fungal infections, in diverse patient populations.

Acknowledgments

We thank Dr. Po-Huang Chyou, Dr. David McClure, and Burney Kieke for analytics support.

Financial support. This work was funded by the Marshfield Clinic Research Institute.

Potential conflicts of interest. All authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

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