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ORIGINAL ARTICLE

The burden of cutaneous disease in solid organ transplant recipients of color

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Organ transplant recipients (OTRs) are at increased risk of cutaneous malignancy. Skin disorders in OTRs of color (OTRoC) have rarely been systematically assessed. We aimed to ascertain the burden of skin disease encountered in OTRoC by prospectively collecting data from OTRs attending 2 posttransplant skin surveillance clinics: 1 in London, UK and 1 in Philadelphia, USA. Retrospective review of all dermatological diagnoses was performed. Data from 1766 OTRs were analyzed: 1024 (58%) white, 376 (21%) black, 261 (15%) Asian, 57 (3%) Middle Eastern/Mediterranean (ME/M), and 48 (2.7%) Hispanic; and 1128 (64%) male. Viral infections affected 45.1% of OTRs, and were more common in white and ME/M patients ($P < .001$). Fungal infections affected 28.1% and were more common in ME/M patients ($P < .001$). Inflammatory skin disease affected 24.5%, and was most common in black patients ($P < .001$). In addition, 26.4% of patients developed skin cancer. There was an increased risk of skin cancer in white vs nonwhite OTRs (HR 4.4, 95% CI 3.5-5.7, $P < .001$): keratinocyte cancers were more common in white OTRs ($P < .001$) and Kaposi sarcoma was more common in black OTRs ($P < .001$). These data support the need for programs that promote targeted dermatology surveillance for all OTRs, regardless of race/ethnicity or country of origin.

KEYWORDS
cancer/malignancy/neoplasia: melanoma, cancer/malignancy/neoplasia: skin—nonmelanoma, clinical research/practice, dermatology, ethnicity/race, immunosuppression/immune modulation, infection and infectious agents—fungal, infection and infectious agents—viral

1 | INTRODUCTION

Organ transplantation is a common and successful treatment for end-stage organ failure. Over 139 024 solid organs were transplanted globally in 2017, an increase of 7.25% on the previous year.[1] The introduction of azathioprine in 1963 made kidney allotransplantation more broadly feasible and the link between immunosuppression and increased risk of cutaneous malignancy was identified shortly afterwards in Australia.[2] Over 80% of organ transplant recipients (OTRs) in Australia[3] and 53% of OTR in the United Kingdom[4]

Catherine A. Harwood and Christina L. Chung share senior authorship.

develop skin cancer within 20 years of transplantation, and the risk of cutaneous squamous cell carcinoma (SCC) is reported to be up to 250 times that of the general population.[3,4] OTRs are also at increased risk of viral, bacterial, and fungal infections.[5]

While direct toxicities of specific immunosuppressive drugs is responsible for some of the skin disorders encountered in OTRs, the reduced immune surveillance caused by these drugs is a key driver for skin infections and malignancies.[6]

Primarily because of the increased risk of skin cancers, policy makers in both the United Kingdom and United States advocate that OTRs should be seen in dedicated surveillance dermatology clinics.[7-9] Much of the research underpinning this advice has been generated in the United States, northern Europe, and Australia and has focused on white OTR populations in whom keratinocyte cancers are more common. However, evidence from South Africa and Saudi Arabia reported Kaposi sarcoma (KS) to occur more frequently in nonwhite populations.[10-12] Furthermore, few studies have systematically detailed nonmalignant skin conditions in OTR of color (OTRoC).

With global migration rising and access to transplant expanding, OTR populations are becoming racially and ethnically more diverse. We designed this study in order to evaluate the spectrum of skin disease among such diverse OTR populations in the United Kingdom and United States. Understanding the consequences of this diversity in terms of variation in malignant and nonmalignant posttransplant skin disease will improve optimal skin care provision and surveillance for all OTRs, regardless of race and skin type.

2 | MATERIALS AND METHODS

2.1 | Patient populations

We performed a review of clinicopathologic data of patients attending posttransplant skin surveillance clinics at 2 large University teaching hospitals where universal screening of OTRs is practiced: Drexel Dermatology Center for Transplant Patients and the Royal London Hospital, Barts Health NHS Trust. Both centers serve racially and ethnically diverse patient populations.[4,13]

2.2 | Data collection

Prospective databases containing all patients seen in the 2 clinics from their initiation (1989 in London; 2011 in Philadelphia) to July 2018 were evaluated and medical records retrospectively searched to validate these data. Data recorded included age at transplant, type of transplant, and self-reported race/ethnicity. Length of follow-up was determined from time of transplant to either last recorded clinic appointment (94%) or close of study (6%). Details of skin disease, including type of cancer and date of histological diagnosis, were confirmed by pathology report when available. Other skin diseases were recorded at date of clinical diagnosis.

2.3 | Statistical analysis

Demographics were compared between each OTR group and between the 2 centers. The groups were compared using ANOVA for continuous and chi-square for categorical variables. Kaplan-Meier (KM) curves were generated for skin cancer–free survival after transplant with statistical significance assessed by log-rank test. Hazard ratios (HRs) with 95% confidence intervals (CIs) for cancer-free survival were estimated, adjusting for self-reported race, age, gender, center, and type of graft organ using a Cox proportional hazard regression model. Odds ratios (ORs) were calculated when statistically feasible. All applied tests were 2 sided and values of $P < .05$ were considered as statistically significant. The statistical analyses were conducted on IBM SPSS 25 and R-studio version 3.6.1.

3 | RESULTS

3.1 | Demographics

In this study, 1806 OTRs under routine surveillance in both centers were identified: 40 were excluded as they were under 18 years old at time of transplant. Of the remaining 1766 OTRs, 1257 were from the London cohort, and 509 were from the Philadelphia cohort; 1128 (64%) were male and 638 (36%) were female.

The centers in London and Philadelphia both serve a racially diverse cohort of OTRs. There were more white OTRs in the London cohort (67.5% vs 34.6%, $P < .001$), whereas there were a higher number of African American/Afro Caribbean/British Caribbean OTRs in Philadelphia (47.5% vs 4.4%, $P < .001$). Although 67.5% of the London cohort was white; demographics have changed over the past 30 years. In 2019, only 34% of patients on the transplant waiting list were white.[14] The London cohort was transplanted at a younger age than the Philadelphia cohort (median 43 years vs 60 years, $P < .001$) and had a longer duration of transplantation (median 10 years vs 5.9 years, $P < .001$). Demographics by center are presented in Table 1.

Date of transplant ranged between June 15, 1969 and January 16, 2018; 1596 (90%) of patients received a kidney or simultaneous kidney/pancreas transplant; 63 (3.6%) received a liver transplant; 59 (3.3%) received a lung or heart transplant; and 48 (2.7%) patients received more than 1 sequential organ transplant (date of first transplant was considered for statistical analysis).

Of the study population, 1024 (58%) patients were white, 376 (21%) were black, 261 (14.8%) were Asian (11.3% South Asian, 2.9% East Asian, 0.6% Southeast Asian), 57 (3.2%) were Middle Eastern/Mediterranean (ME/M), and 48 (2.7%) were Latino. Median (interquartile range [IQR]) age at transplantation was 47 (35.7-58) years. ME/M patients were transplanted at a younger age than other groups ($P < .001$). Median (IQR) duration of transplantation was 9 (4-16.6) years. White and ME/M patients had a longer duration of transplantation than black and Latino patients ($P < .001$). Demographics and skin disease diagnoses by race are presented in Table 2.

TABLE 1 Demographics by center

	London cohort	Philadelphia cohort	*P*-value
Age at transplant, y, median (IQR)	43.0 (32.0-53.0)	60.0 (49.0-66.0)	<.001
Period of observation	1989-2018	2009-2018	
Male	801 (63.7%)	327 (64.2%)	.8
Race/ethnicity			
White	848 (67.5%)	176 (34.6%)	<.001
Black	131 (10.4%)	245 (48.1%)	
AA/AC/BC	55 (4.4%)	242 (47.5%)	
A/BA	76 (6%)	3 (5.9%)	
Middle Eastern	56 (4.5%)	1 (0.2%)	
Latino/Hispanic	0	48 (9.4%)	
Asian	222 (17.7%)	39 (7.7%)	
Duration of transplantation (y), median (IQR)	10.0 (5.0-19.0)	5.9 (2.2-11.2)	<.001
Type of transplant			
Kidney or kidney/pancreas	1224 (97.4%)	372 (73.1%)	<.001
Liver	3 (0.2%)	60 (11.8%)	
Lung/heart	24 (1.9%)	35 (6.9%)	
Multiple organ	6 (0.5%)	42 (8.3%)	

Note: $P < .05$ is statistically significant, ANOVA or chi-square.
Abbreviations: AA/AC/BC, African American, Afro Caribbean, British Caribbean; A/BA, African, British African.

3.2 | Overall burden of disease

There was a high prevalence of skin disease in all patients following transplant, regardless of race; 1337 (75.7%) patients were diagnosed with at least 1 skin condition. White and ME/M OTRs had the highest burden of disease (82% and 84%, respectively) than other groups ($P < .001$).

3.3 | Skin cancer

Overall, 467 (26.4%) patients were diagnosed with at least 1 cutaneous malignancy (including SCC in situ [SCCIS]). Median (IQR) time from transplantation to diagnosis of first skin cancer was 8.4 years (4-13.5). Patients with skin cancer had a longer duration of transplantation than those who did not have skin cancer (273 vs 176 months, $P < .001$). Skin cancer was diagnosed in 409 (39.9%) of white OTRs, higher than black (7.2%), ME/M (12.3%), Latino (12.5%), and Asian (6.9%) ($P < .001$) (Table 2).

We conducted KM analysis for cancer-free survival among the racial groups (Figure 1). Compared to white OTRs, all other racial groups had a reduced risk of skin cancer ($P < .001$). Cancer-free survival in years (mean ± standard error) was lower in white OTRs (18.1 ± 0.6), than black (24.5 ± 0.8), ME/M (32.6 ± 1.9), Latino (23.1 ± 1.6), and Asian (34.4 ± 1.5) ($P < .001$).

We then conducted Cox regression analysis to evaluate the effects of covariates on the HR of developing skin cancer (Figure 2). First, we conducted a univariate Cox regression for white vs nonwhite OTRs, which showed higher risk of cancer in white than in nonwhites (HR 4.4, 95% CI 3.5-5.7, $P < .001$). Then we conducted multivariate Cox regression, with ethnicity, age at transplant, gender, center, and type of transplant included in the model. With white OTRs as the reference group, the rate of cancer was much lower in the other groups: black (HR 0.28, 95% CI 0.18-0.43), ME/M (HR 0.30, 95% CI 0.14-0.63), Latino (HR 0.38, 95% CI 0.16-0.88), and Asian (HR 0.15, 95% CI 0.09-0.24). With each 1-year increase in age at transplant, the HR increased by 1.05 (95% CI 1.04-1.06) ($P < .001$). There was a trend toward a lower risk of skin cancer in females than in males (HR 0.82, 95% CI 0.67-1.00) ($P = .051$). Patients from the London cohort were more likely to be diagnosed with skin cancer than the Philadelphia cohort (HR 1.95, 95% CI 1.382-2.75, $P < .001$). OTRs with multiple transplanted organs had a reduced risk of skin cancer (HR 0.48, 95% CI 0.238-0.99, $P = .046$).

The incidence of skin cancers in the nonwhite OTRs was less than in the white OTRs, but there was a notable difference in the Asian cohort in that, on logistic regression, East Asian OTRs had higher OR 5.1 (95% CI 1.8-14.1) for skin cancer compared to South Asians ($P < .001$).

3.3.1 | Keratinocyte cancers (KC) and premalignant skin disease

We observed a total of 1644 invasive SCCs in 255 patients. A total of 165 OTRs had multiple (≥2) tumors. SCC affected 246 (24%) of the white cohort; 97% of all SCC diagnoses were made in white patients, higher than in any other group ($P < .001$). One or more SCCIS was observed in 251 of all patients, independent of whether invasive SCC was later diagnosed. We observed a total of 882 basal cell carcinomas (BCCs), affecting 255 patients, resulting in an overall ratio of 1:1.86 BCC:SCC (1:1.88 in white, 4:1 in ME/M, 1:1 in black and Asian). In addition, 137 patients had multiple BCCs. SCCIS and BCC also affected white OTRs more than patients from other racial groups ($P < .001$).

Actinic keratoses (AKs) are regarded as SCC precursor lesions, but in contrast to SCCIS, less than 0.1% will progress to SCC. Their diagnosis is almost always clinical rather than histological.[15] For these reasons, recording of AK incidence and prevalence was less consistent than for SCC, BCC, and SCCIC. We therefore did not include AK in the final dataset.

3.3.2 | Melanoma

Eleven invasive melanomas were diagnosed, all of which occurred in white patients.

TABLE 2 Demographics and skin diagnoses by race

Characteristics	Race or ethnic group						*P*-value
	All (n = 1766)	White (n = 1024, 58%)	Black (n = 376, 57%)	Middle Eastern and Mediterranean (n = 57, 3.2%)	Latino/Hispanic (n = 48, 2.7%)	Asian (n = 261, 14.8%)	
Age at transplant, y median (IQR)	47.0 (35.7-58.0)	46.0 (34.0-57.0)	53.0 (42.0-62.0)	40.0 (28.0-50.0)	57.5 (42.2-64.0)	44.0 (34.0-55.0)	<.001
Male	63.9%	64.7%	59.6%	66.7%	66.7%	65.5%	.4
Organ transplant type							
Kidney or kidney/pancreas	90.4%	90.5%	89.1%	93.0%	60.4%	96.6%	<.001
Liver	3.6%	3.2%	2.7%	1.8%	31.3%	1.5%	
Lung/heart	3.3%	4.3%	2.1%	1.8%	2.1%	1.9%	
Multiple organs	2.7%	2.0%	6.1%	3.5%	6.3%	0%	
Duration of transplant, y, median (IQR)	9.0 (4.0-16.6)	10.9 (5.2-19.0)	5.7 (2.1-10.6)	10.0 (4.6-20.2)	7.4 (2.1-15.8)	7.3 (3.8-15.7)	<.001
Overall prevalence of skin disease posttransplant, %	75.7%	81.9%	62.0%	84.2%	54.2%	73.2%	<.001
Skin cancer							
Any skin cancer posttransplant, n (%)	467 (26.4)	409 (39.9)	27 (7.2)	7 (12.3)	6 (12.5)	18 (6.9)	<.001
SCC, n (%)	255 (14.4)	246 (24.0)	3 (0.8)	1 (1.8)	0	5 (2.0)	<.001
BCC, n (%)	255 (14.4)	244 (23.8)	3 (0.8)	4 (7.0)	1 (2.1)	5 (1.1)	<.001
SCCIS, n (%)	251 (14.2)	231 (22.6)	7 (1.9)	4 (7.0)	5 (2.0)	4 (1.6)	<.001
Melanoma, n (%)	11 (0.6)	11 (1.1)	0	0	0	0	.09
KS, n (%)	16 (0.9)	1 (0.1)	13 (3.5)	1 (1.8)	0	1 (0.4)	<.001
Other skin cancer, n (%)[a]	40 (2.3)	31 (3.0)	2 (0.5)	1 (1.8)	0	6 (2.3)	.06
Transplant to first skin cancer, y, median (IQR)	8.4 (4.0-13.5)	8.6 (4.3-13.7)	4.5 (1.2-10.1)	3.0 (2.7-9.9)	5.5 (2.5-14.0)	7.1 (4.0-23.8)	.059
Nonmalignant lesions							
Viral infections, n (%)	796 (45.1)	563 (55.0)	95 (25.3)	28 (49.1)	9 (18.8)	101 (38.7)	<.001
Fungal infection, n (%)	497 (28.1)	268 (26.2)	92 (24.5)	29 (50.9)	12 (25.0)	96 (36.8)	<.001
Inflammatory disease, n (%)	423 (24.5)	219 (21.4)	113 (30.1)	13 (22.8)	12 (25.0)	75 (28.7)	<.001
Sebaceous hyperplasia, n(%)	281 (15.9)	221 (21.6)	8 (2.1)	17 (29.8)	2 (4.2)	33 (12.6)	<.001

Note: $P < .05$ is statistically significant, ANOVA or chi-square.

Abbreviations: BCC, basal cell skin cancer; KS Kaposi sarcoma; SCC, squamous cell skin cancer; SCCIS, squamous cell carcinoma in situ.

[a]Cutaneous appendageal tumors (28), Merkel cell carcinoma (2), dermatofibrosarcoma protuberans (2), mycosis fungoides (1).

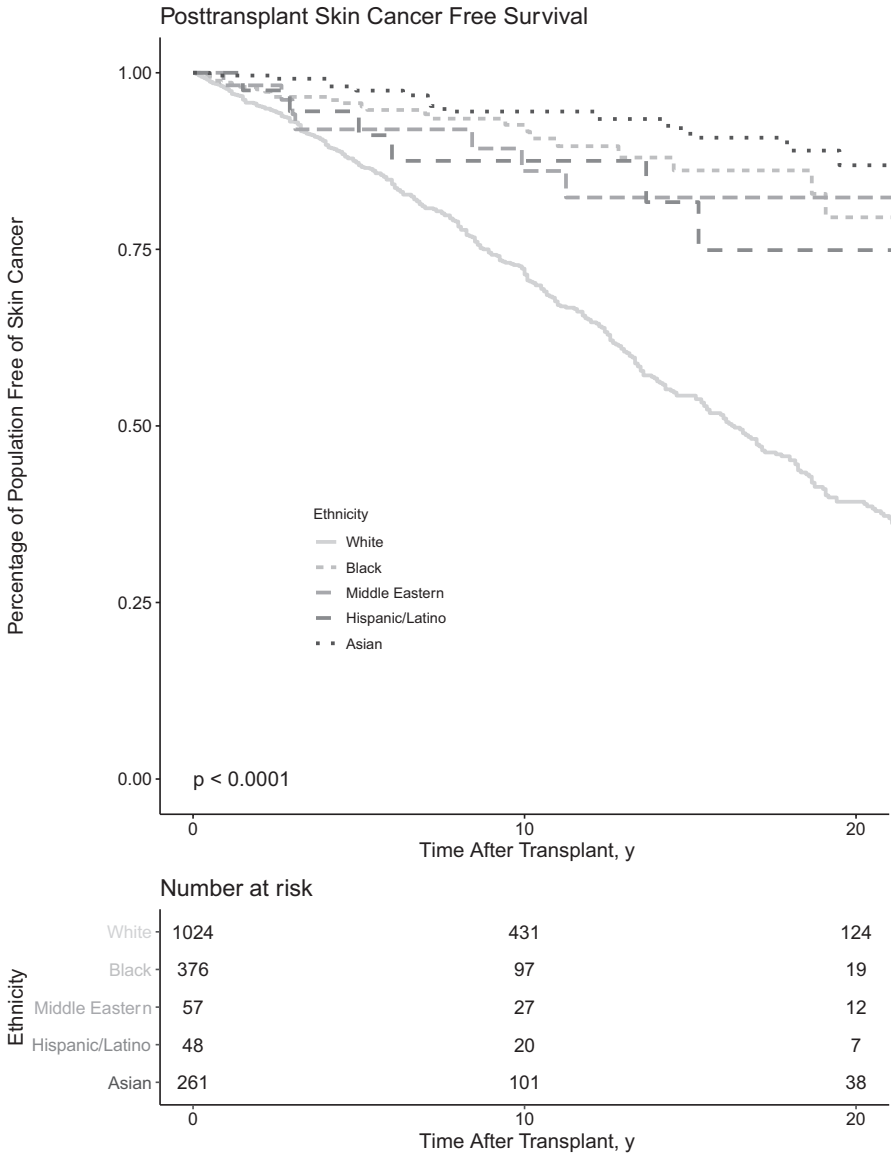

FIGURE 1 Posttransplant skin cancer (including squamous cell carcinoma in situ)–free survival by race, time in years

3.3.3 | Kaposi sarcoma (KS)

KS was more common in the black cohort, with 13 of the total 16 cases being diagnosed in black African OTRs ($P < .001$), all of whom were born in sub-Saharan Africa. All cases except 1 were diagnosed in the London cohort. Median (IQR) time from transplantation to onset of KS was 15 (6-36) months.

3.3.4 | Other skin cancers

Twenty-eight cutaneous appendageal tumors (AT) were diagnosed and included 12 porocarcinomas, 9 sebaceous carcinomas, 2 squamous eccrine ductal carcinomas, 2 microcystic adnexal carcinomas, and 1 each of eccrine nodular carcinoma, apocrine adenocarcinoma and sweat duct carcinoma. Two cases of Merkel cell carcinoma (MCC) and 2 cases of dermatofibrosarcoma protuberans were diagnosed. Although affecting predominantly white patients, there were no significant differences in disease incidence between races.

3.4 | Nonmalignant skin disease

Nonmalignant dermatoses were common in all patients (Table 3); 1236 (70%) of patients were diagnosed with at least 1 condition. Bacterial infections were excluded from the analysis, as they usually occur acutely and were often treated in the community.

3.4.1 | Viral infections

White and ME/M patients had a higher incidence of viral infections ($P < .001$). Viral warts were common (737 cases, 41.7%), and affected white OTRs more than other groups ($P < .001$). The presence of viral

warts was associated with an increased incidence of both invasive SCC and SCCIS ($P < .001$). Other infections included herpes simplex virus (HSV) (59 cases, 3.3%), herpes zoster virus (HZV) (49 cases, 2.8%), varicella zoster virus (VZV) (6 cases, 0.3%), and molluscum contagiosum (28 cases, 1.6%).

3.4.2 | Fungal infections

The overall incidence of fungal infections was higher in ME/M patients than in other racial groups ($P < .001$). Pityriasis versicolor (PV) (165 cases, 9.3%) occurred most frequently in Asian OTRs ($P < .001$). Onychomycosis (194 cases, 11%) was more common in the ME/M group ($P < .001$). Tinea pedis (217 cases, 12.3%) was diagnosed more frequently in black OTRs ($P < .001$), whereas nonpedal tinea (63 cases, 3.6%) was more common in ME/M and Asian OTRs ($P < .001$).

3.4.3 | Inflammatory skin disease

We observed 135 cases of dermatitis (7.6%): this included cases diagnosed clinically or histologically as atopic, allergic contact, irritant contact, dyshidrotic, stasis, asteatotic, or nummular dermatitis. Dermatitis was most common in black OTRs ($P < 0001$). Overall incidence of psoriasis was low (35 patients, 1.4%). Acneiform eruptions (AEs) were recorded in 305 patients (17.3%). Overall, black OTR had the highest incidence of inflammatory skin disease ($P < .001$).

3.4.4 | Miscellaneous skin disease

We observed 281 cases of multiple (≥5) sebaceous hyperplasia (SH) (15.9%), with the highest incidence in white and ME/M patients ($P < .001$). Frequencies of other skin conditions were too low to undertake comparative statistical analysis.

4 | DISCUSSION

This international study has shown a high incidence of cutaneous disease in OTRs of all races. Although the race-specific risk of KC and KS has been well documented, the incidence of other skin disease has not been fully explored by previous studies. Immunosuppression-associated reductions in cell-mediated immunity led to increased risk of infection: fungal infections are more common and there is reduced control of viral replication with consequent increased incidence of viral infections and virally driven cancers such as KS, MCC, anogenital SCC, and potentially cutaneous SCC. In addition, immunosuppressants act synergistically with ultraviolet radiation (UVR) to promote carcinogenesis, both by impairing recognition and elimination of malignant cells and also through direct carcinogenic effects.[6]

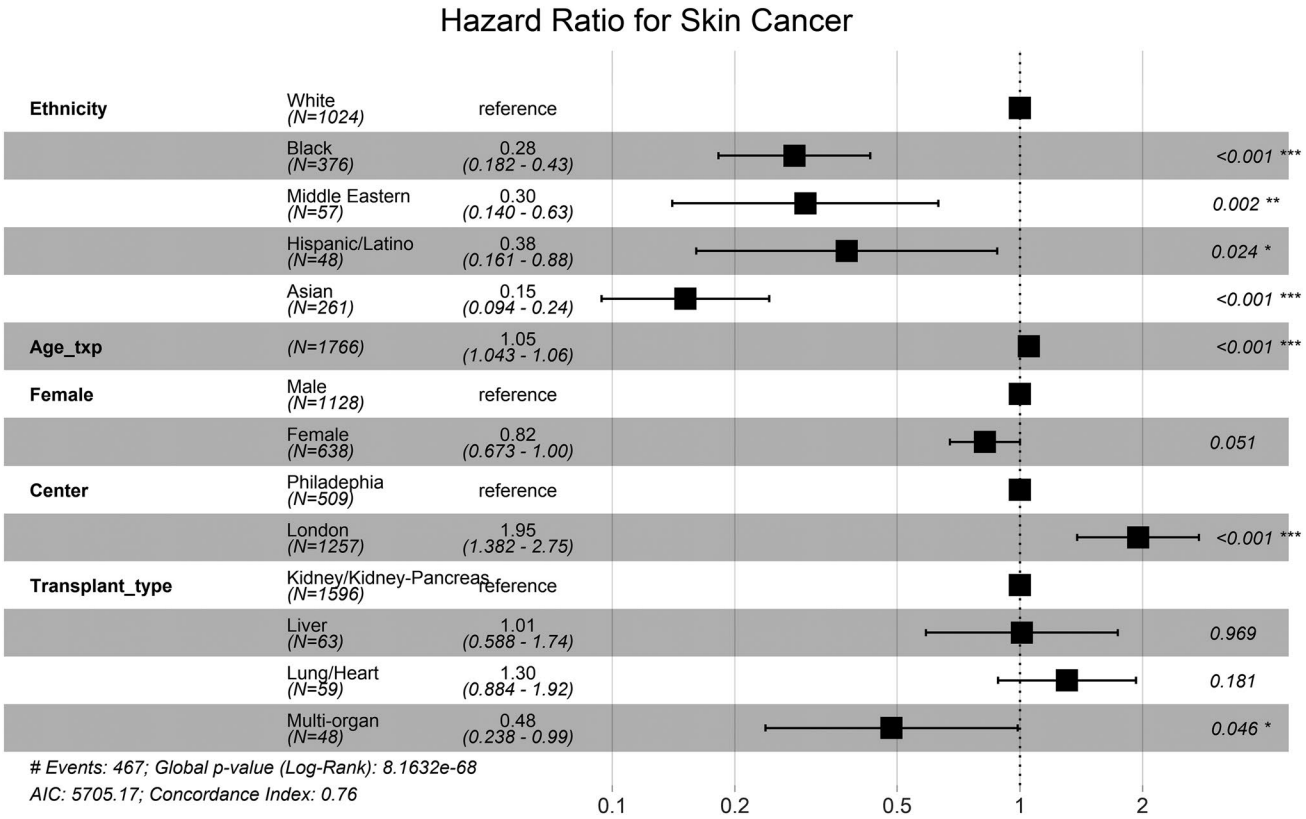

FIGURE 2 Forest plot of multivariate analysis of hazard ratios for developing skin cancer using a Cox proportional hazard regression model

TABLE 3 Infectious and inflammatory skin disease by race

Condition	Race or ethnic group						
	All (n = 1766)	White (n = 1024, 58%)	Black (n = 376, 57%)	ME/M (n = 57, 3.2%)	Latino/Hispanic (n = 48, 2.7%)	Asian (n = 261, 14.8%)	*P*-value
Viral infections							
Viral warts	737 (41.7%)	532 (52%)	74 (19.7%)	28 (49.1%)	8 (16.7%)	95 (36.4%)	<.001
HSV	59 (3.3%)	39 (2.8%)	11 (2.9%)	3 (5.3%)	1 (2.1%)	5 (1.9%)	.49
HZV	49 (2.8%)	31 (3%)	12 (3.2%)	1 (1.8%)	0	5 (1.9%)	.6
VZV	6 (0.3%)	4 (0.4%)	2 (0.5%)	0	0	0	.7
Molluscum contagiosum	28 (1.6%)	19 (1.9%)	3 (0.8%)	0	0	6 (2.3%)	.3
Fungal infections							
Pityriasis versicolor	165 (9.3%)	98 (9.6%)	15 (4%)	13 (22.8%)	0	39 (14.9%)	<.001
Onychomycosis	194 (11%)	120 (11.7%)	26 (6.9%)	13 (22.8%)	1 (2.1%)	34 (13%)	<.001
Tinea pedis	217 (12.3%)	106 (10.4%)	65 (17.3%)	8 (14%)	9 (18.8%)	29 (11.1%)	.006
Tinea (non-pedal)	63 (3.6%)	32 (3.1%)	9 (3.4%)	5 (8.8%)	2 (4.2%)	(155.7%)	.04
Inflammatory conditions							
Dermatitis	135 (7.6%)	65 (6.3%)	43 (11.4%)	2 (3.5%)	7 (14.6%)	18 (6.9%)	.005
Psoriasis	25 (1.4%)	16 (1.6%)	4 (1.1%)	0	2 (4.2%)	3 (1.1%)	.4
Acneiform eruption	305 (17.3%)	158 (15.4%)	75 (19.9%)	11 (19.3%)	5 (10.4%)	56 (21.5%)	.055

Note: $P < .05$ is statistically significant, chi-square.

Abbreviations: HSV, herpes simplex virus; HVZ, herpes zoster virus; ME/M, Middle-Eastern/Mediterranean; VZV, varicella zoster virus.

The current pandemic of coronavirus 2019 (COVID 19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) poses a new threat to OTRs. Although cutaneous manifestations of COVID-19 are recognized, there have been no reports to date specifically related to OTRs. In addition, while the higher rates of intensive care admission and death in OTRs support the importance of the current recommendation for "shielding,"[16,17] there are also concerns that this may result in delayed diagnosis and treatment of significant cutaneous infections and malignancy.

4.1 | Skin cancer risk factors

Our study confirms that white OTRs have the highest risk of skin cancer.[18,19] However, we also found the rate of skin cancer in OTRoC to be more than double that previously reported (6.9%-12.5% vs 0%-5%).[20-23] The overall median time to onset of skin cancer was 8.4 years. This was shortest for black patients, mainly because the time to diagnosis was shortest for KS, although this did not quite reach significance ($P = .059$).

The HR for skin cancer in the London cohort was almost double that of the Philadelphia cohort (1.95), even when adjusting for covariates including race and duration of transplantation. Reasons for this are unclear and our analysis is unable to exclude the possibilities that this may relate to differences in skin phototype, cumulative lifetime UVR exposure, or differences in immunosuppressive drug regimens used in the respective centers.

We observed a trend toward reduced risk of skin cancer in female OTRs. Male sex has previously been reported as a risk factor for skin cancer in OTRs.[24] This may relate, in part, to photoprotective behavior and occupational UVR exposure.[25,26]

Multiorgan transplant recipients appeared to have a reduced risk of skin cancer in this study, though the CI was wide. The reasons for this are unclear.

4.1.1 | Keratinocyte cancers and premalignant skin disease

Invasive SCC was the most common cancer in OTRs. UVR is the main driver for the increased incidence of SCC and BCC observed in OTRs through its mutagenic and immunosuppressive effects.[5,17] Additional cofactors include direct carcinogenic effects of immunosuppressive medications (including azathioprine and cyclosporine), other medication often used posttransplant (such as voriconazole) and human papillomavirus (HPV) infection.[6,27,28] Consistent with the key role for UVR, we observed the highest incidence in white patients with lighter skin phototypes.[29] When subgroup analysis of the Asian cohort was performed, we observed an OR of 5.1 for East Asians developing skin cancer when compared to South Asians, likely reflecting known differences in Fitzpatrick skin phototype between these populations.[30]

SCC rates in the general population have been rising, resulting in a BCC:SCC ratio of around 2.5:1 in the United States in 2018.[31] This ratio is reversed in OTRs.[32] We observed a ratio of

1:1.86 (882:1644), but this reversed ratio was only observed in white OTRs. Studies from Spain and Italy have shown BCCs to be more common than SCCs in Mediterranean OTRs.[33,34] Darker skin phototypes may therefore provide greater protection against SCC than BCC.

4.1.2 | Melanoma

Incidence of melanoma in OTRs is reported to be 2-3 times that of the general population.[35] It disproportionately affects white populations, and no OTRoC developed invasive melanoma in this study, although the small numbers of cases meant that this did not reach significance.[36]

4.1.3 | Kaposi sarcoma

Most posttransplant KS is the result of reactivation of latent human herpesvirus 8 (HHV8), possibly as a consequence of immunoparesis following induction and maintenance immunosuppression, which allows uncontrolled HHV8 replication.[37] Incidence is reported to be 500 times higher in OTRs and reflects the seroprevalence of HHV8 which is >50% in sub-Saharan Africa, and <5% in northern Europe and America.[38] Thus, KS was more common in black OTRs in the London cohort, the majority of whom originated from HHV8-endemic regions of sub-Saharan Africa. In contrast, most black patients in the Philadelphia cohort originated from the United States and their KS rates were not increased. The 1 patient diagnosed with KS in the Philadelphia cohort was also born in sub-Saharan Africa. Median time to diagnosis of KS was 15 months. This is shorter than for other skin cancers and a consequence of reactivation of latent rather than acquired HHV8 infection driving this malignancy.[39-41]

4.1.4 | Other skin cancers

ATs are rare in the general population; however, the standard incidence ratio for ATs in OTRs is reported as 40.[42,43] We observed 28 ATs in our study, a higher prevalence than expected in the general population. The majority occurred in white OTRs. Although both cyclosporine and azathioprine have been implicated in sebaceous tumor development,[44,45] the pathogenesis of many ATs is not well understood, and UVR, immunosuppression, and viral pathogens may all be contributory.[46] The incidence of MCC is reported to be 24 times higher in OTRs, and we observed 2 cases of MCC in our study, both in white OTRs.[47] Impaired T cell function and UVR are proposed to drive unregulated transcription of causative Merkel cell polyomavirus (MCPyV) and MCC pathogenesis.[47] Seroprevalence of MCPyV in the general population is reported to be high (60%-81%) in studies conducted across Europe, China, and Africa.[48-51]

4.2 | Nonmalignant skin disease

4.2.1 | Viral infections

Viral warts are the most common cutaneous infection in OTRs, as confirmed in our study.[52,53] The overall rate of clinical HPV infection was 42% and white OTRs were the most affected. Reduced UVR susceptibility and differences in cellular structure of the dermis and epidermis may play a role in racial susceptibility to HPV.[54] We also observed that patients diagnosed with viral warts had a higher incidence of both SCCIS and invasive SCC. Previous studies have indicated that OTRs have an increased HPV diversity, multiplicity, and viral load, and this is associated with an approximately 2-fold increased risk of SCC.[55] In addition, the high burden of HPV infection in all races should also alert clinicians to an increased risk of HPV-driven SCC in the anogenital region, to which OTRoC appear to be disproportionately affected.[6,20,56]

We observed apparently low rates of both HSV (3.3%) and HZV (2.8%) when compared to the literature. Both HSV and HZV occur early in the posttransplant period due to reactivation of latent virus on introduction of immunosuppression, and may be under-reported in this study due to the acute and transient nature of infection.[52,57-59] Molluscum contagiosum, caused by DNA poxvirus, was also uncommon (1.6%) but consistent with previous studies reporting rates of up to 3%.[52,60]

4.2.2 | Fungal infections

OTRs have fewer Langerhans cells in the epidermis, and chronic corticosteroid therapy results in thickening of the stratum corneum and delayed desquamation; both of which may be contributory in developing superficial fungal infections.[61,62]

Overall incidence of fungal infections was higher in ME/M OTR than any other racial group in our study. Case-control studies have found that PV was the most common superficial mycosis observed in OTR with a prevalence of 18%-34%.[63,64] We observed an increased incidence of PV in Asian OTR. Studies in tropical countries have reported prevalence up to 50%, while those performed in Scandinavia report a prevalence of only 1%.[65-68] This disparity may be the result of varying temperature and humidity levels providing a favorable environment for yeasts. However, it is also possible that PV is more readily diagnosed in darker skin as the associated hypopigmentation is clinically more prominent than in lighter skin types.

Onychomycosis has been reported to affect OTRs more frequently than matched controls.[63,69] Onychomycosis was most common in the ME/M cohort, whereas tinea pedis was most common in black patients. Dermatophyte infection affecting areas other than the feet were more common in ME/M and Asian OTR. The reasons for this are not clear.

4.2.3 | Inflammatory skin disease

Most inflammatory dermatoses, such as dermatitis and psoriasis, are uncommon in OTRs due to the immunosuppressive effects of chronic antirejection therapy, and the rates that we observed were lower than those reported in the general population.[70-73] However, OTRs frequently develop drug-induced AEs following transplantation. Acne may be caused by corticosteroids, cyclosporine, mycophenolic acid agents, and sirolimus.[74] Patients originating from high-incidence countries receive antituberculous prophylaxis with isoniazid for at least 1 year posttransplant, which is well known to provoke AEs.[75,76] We observed increased incidence of dermatitis in black OTRs. Previous epidemiological studies of the general population have shown increased incidence of atopic dermatitis in African American and British Caribbean children in both the United States and London.[77,78]

4.2.4 | Miscellaneous skin disease

We identified multiple SH in 15.9% of our cohort, consistent with previous studies that have reported SH in 15%-30% of OTRs, compared with 1% of age- and sex-matched controls. However, previous studies have not evaluated racial differences in SH prevalence: we saw the greatest incidence in white OTRs, but other races were also affected. Multiple SH is appears to occur most commonly in male OTRs treated with cyclosporine, a highly lipophilic molecule that may directly influence pilosebaceous unit architecture.[79,80]

4.3 | Strengths and limitations

The strengths of this study include the racial diversity of subjects, comprehensive data analysis and long follow-up period.

We acknowledge a number of limitations. A major confounder of this study is the inevitable variability of immunosuppressive regimens both between centers as well as between patients, and within the same patient over the duration of the study period. In addition, the influence of an "era effect"—that is, the effect of changes in immunosuppressive regimens used over the timespan of this study (1989-2018) may also be relevant. OTRs transplanted pre-1984 received azathioprine and corticosteroids as a standard maintenance immunosuppressive regimen, and after 1984 cyclosporine was introduced. From the late 1990s, azathioprine was largely replaced with mycophenolate mofetil, tacrolimus was used as an alternative calcineurin inhibitor and mTOR inhibitors were introduced.[81] There is evidence that azathioprine may be associated with an increased risk of SCC when compared to newer antimetabolites such as mycophenolic acid agents and mTOR inhibitors are associated with a lower risk.[81,82] We have previously assessed the potential impact of such "era effects" on skin cancer risk in the London cohort and found no significant era effect at least for transplantation pre-1985 vs 1985-2000 (*P*-value for trend .895).[4] However, in view of these confounding factors, and also given the inherent challenge of assessing individual immunosuppressive burden, we did not analyze in detail the association between immunosuppressive drug regimens and skin disease in the current study. Nonetheless, we acknowledge that such differences may have contributed to our observed patterns of skin disease susceptibility.[83] The impact of immunosuppressive drug regimens on inflammatory and infective skin disease is also uncertain and is a potentially important risk factor to evaluate in future prospective studies.

Another potential confounder in this study is the self-reporting of race, which is recognized to be an inaccurate predictor of Fitzpatrick skin phototype.[84] The latter influences susceptibility to UVR and skin cancer risk but was not reported in this study.

The inherent limitations of a retrospective study that is not strictly population-based further limit interpretation of the findings of our study. In particular, the acute nature of many bacterial and some viral infections meant that these were not systematically and fully recorded, particularly when diagnosed and treated in the community. A future prospective, population-based case-controlled study would strengthen the evidence provided by these data.

5 | CONCLUSIONS

All racial groups are at risk of developing skin disease, but the nature and timing of these disorders vary. The patterns of susceptibility to skin disease in OTRs of different racial groups identified in this study will provide important evidence for rationalizing design of targeted dermatology surveillance programs. These data will also inform development of tailored education resources for patients and health care providers for both recognition and optimal management of skin conditions encountered following solid organ transplantation across all racial groups.

DISCLOSURE

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation*.

DEDICATION

We dedicate this manuscript to the memory of our dear friend, ITSCC President, and accomplished scientist, Oscar Colegio, MD, PhD. Oscar's passion for discovery led him to be a pioneer in the advancement of medical knowledge of posttransplant cutaneous disease. He was a prolific contributor to our community who hailed from his beloved McAllen, Texas. A proud Mexican-American, Oscar embraced persons across all walks of life and was a steadfast champion of our work with organ transplant recipients of color. May his vibrant spirit live on through these works.

DATA AVAILABILITY STATEMENT

The datasets generated during and/or analyzed during this study are available from the corresponding author on reasonable request.

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