SKIN

BRIEF ARTICLE

Predicting Skin Cancer Development after Liver Transplant

Chelsea Shope, MSCR[1], Laura Andrews, MSCR[1], Courtney Linkous, BA[1], Pelin Sagut, MD[2], Lara Wine Lee, MD, PhD[2]

[1]College of Medicine, Medical University of South Carolina, Charleston, SC
[2]Department of Dermatology & Dermatologic Surgery, Medical University of South Carolina, Charleston, SC

ABSTRACT

Introduction: As the number of solid organ transplants (SOTs) continues to increase and post-transplant therapies improve, SOT recipients (SOTRs) live longer and thus, are increasingly affected by post-transplant sequala such as skin cancer. Research investigating risk factors associated with skin cancer development in SOTRs has largely been conducted in kidney recipients.
Methods: We performed a retrospective chart review of SOTRs seen by dermatology from January 1, 2012 – June 1, 2022. Patients were referred due to specific skin complaints or for concerning lesions. Data was analyzed using Pearson chi-square testing and Classification and Regression Tree (CART) modeling.
Results: Of 530 patients meeting inclusion criteria, 80 received liver transplants. Among liver recipients, a total of 155 skin cancers and five recurrences developed following transplant among 37 patients (46.3%) with skin cancer diagnosis occurring within a mean of 3.6 years. 35 (94.6%) were Caucasian and the remaining two were African American. Patients who developed skin cancer were significantly more likely to be male (78.4%, p-value=0.045) and former smokers (59.5%, p-value=0.038). CART showed age greater than 43 years was the biggest predictor for later skin cancer development. Patients most frequently developed squamous cell carcinoma (60.9%) of the head and neck (51.4%) or upper extremities (29.7%).
Conclusion: Risk factors associated with skin cancer development in liver transplant recipients include increased age at transplant, male sex, and smoking status. Stratification of referrals to dermatology based on these factors should be considered.

INTRODUCTION

Increases in SOT recipients (SOTR) [1]and post-transplant survival have increased the number of patients affected by chronic immunosuppression. Sequalae includes increased risk for malignancies, most commonly skin cancer.[2] Risk of skin cancer is correlated with type of organ transplanted,[3] however, the majority of literature elucidating skin cancer risk is in kidney recipients.[4] While liver recipients is reported as lowest risk for skin cancer, there is less data compared to kidney graft recipients, and the incidence rates reported are wide.[5] We sought to describe the incidence and associated risk factors for skin cancer in liver transplant recipients at our institution. Further characterizing skin cancer incidence in this

cohort may help risk stratify patients, allowing for efficient use of resources.[6]

METHODS

Following IRB approval, we conducted a retrospective review of SOTRs at our institution between January 1, 2012, and June 1, 2022. SOTRs who were seen by transplant and dermatology at our institution were included. These patients were referred due to skin complaints or presence of concerning skin lesions. Information regarding patient demographics, comorbid conditions, family history, transplant course, and dermatologic course were collected.

Data analysis was performed using SPSS Statistics 28 (IBM, Armonk, NY). Descriptive statistics were used to characterize the patient population. Categorical data was evaluated using Pearson chi-square testing. Classification and Regression Tree (CART) modeling was used to assess risk for skin cancer development. CART modeling adds variables of interest to the regression model in a univariate manner. Variables included in CART analysis were sex, age at transplant, race, smoking status, comorbid conditions, and transplant-associated medications. CART uses significant variables to the build a multivariate regression model, as well as Z counts and estimated marginal means.

RESULTS

We identified 530 patients who underwent SOT and were seen by dermatology, of which 80 received liver transplants. Mean age at transplant was 52.65 years. The majority were Caucasian (90.0%) and male (67.5%). Half of recipients were non-smokers (**Table 1**).

Among liver recipients, 37 (46.3%) developed skin cancer post-transplant, with a mean time to first skin cancer diagnosis of 3.6 years. They had a mean age of 57.7 [$\pm$7.6] years at transplant, as compared to a mean age of 47.6 [$\pm$22.8] years in liver recipients who did not develop skin cancer (p-value $\leq$0.001). Skin cancer most commonly developed in males (78.4%, p-value=0.045) and former smokers (59.5%, p-value=0.038) (Table 1). Skin cancer occurred most frequently among Caucasian patients (35, 94.6%). Among African American patients who developed skin cancer (2), both patients were male, former smokers who developed BCC on the face.

A total of 155 skin cancers and five recurrences developed among 37 liver recipients. First skin cancers were most frequently SCC (67.6%), BCC (29.7%), or melanoma in situ (MIS) (2.7%). Among SCCs, 44.0% were invasive at the time of diagnosis. Skin cancers were most commonly found on the head and neck (51.4%, including scalp, face, ear, and neck) or upper extremities (29.7%). Further characterization of these skin cancers is provided (**Table 2**). Subsequent skin cancers occurred in 23 of 37 liver recipients (62.2%) with recurrence in one patient. Second skin cancers were also most commonly SCC (14, 60.9%) or BCC (9, 39.1%). In total, there were 101 SCCs, 49 BCCs, and 5 MMs. No Merkel cell carcinomas, Kaposi sarcomas, or porocarcinomas were reported.

CART demonstrated that age greater than 43 years was the strongest predictor for later skin cancer development in this cohort. Among patients less than 43 years of age, Caucasian race and older age at transplant were most strongly correlated with skin cancer development. The following were not predictors of post-transplant skin cancer development: hypertension, type 2 diabetes

Table 1. Liver transplant recipient patient demographics

	All Liver Transplant Recipients	Liver Transplant Recipients with Skin Cancer	Liver Transplant Recipients without Skin Cancer	p-value
Age at transplant (years)	52.65	57.73	47.57	<0.001*
Race (count, %)				0.186
African American	8 (10.0%)	2 (5.4%)	6 (14%)	
Caucasian	72 (90.0%)	35 (94.6%)	37 (86%)	
Sex (count, %)				0.045*
Female	26 (32.5%)	8 (21.6%)	18 (41.9%)	
Male	54 (67.5%)	29 (78.4%)	25 (58.1%)	
Smoking Status (count, %)				0.031*
Never Smoker	40 (50%)	13 (35.1%)	27 (62.8%)	
Current Smoker	4 (5%)	2 (5.4%)	2 (4.7%)	
Former Smoker	36 (45%)	22 (59.5%)	14 (32.6%)	
Family History of Skin Cancer (count, %)				0.428
Yes	5 (6.3%)	3 (8.1%)	2 (4.7%)	
No	75 (93.8%)	34 (91.9%)	41 (95.3%)	

*Indicates statistically significant result ($p \leq 0.05$)

Table 2. First skin cancers among liver transplant recipients

Type of Skin Cancer	Count (%)
Squamous Cell Carcinoma	25 (67.57%)
*SCCis**	14 (56.0%)
Invasive[+]	11 (44.0%)
Low Risk	5 (45.45%)
High risk	5 (45.45%)
Very high risk	1 (9.1%)
Basal Cell Carcinoma	11 (29.73%)
Melanoma in situ	1 (2.70%)
Location of Skin Cancer	**Count (%)**
Scalp	6 (16.22%)
Face & Neck	11 (29.73%)
Ear	2 (5.41%)
Upper extremities	11 (29.73%)
Chest or back	2 (5.41%)
Lower Extremities	2 (5.41%)
Other	3 (8.11%)

*SCCis: Squamous Cell Carcinom in situ. [+]Low risk: trunk/extremities, <2 cm OR well/moderately differentiated, <6 mm deep. High risk: trunk/extremities, 2 - 4 cm OR anywhere on head/neck. Very high risk: any site >4 cm OR poorly differentiated, >6 mm deep, or perineural/lymphatic involvement.

mellitus, hyperlipidemia, chronic kidney disease, cardiomyopathy or coronary artery disease, hepatitis, nonalcoholic fatty liver disease, and cirrhosis. Tacrolimus, mycophenolate mofetil (MMF), azathioprine, val/acyclovir, and Cyclosporine (CsA) use as part of the post-transplant therapeutic regimen were not significant predictors for skin cancer, though CsA use post-transplant approached significance as a risk factor for skin cancer (p-value=0.063).

DISCUSSION

It is well established that SOTRs are at increased risk for skin cancer. In all SOTRs, the factors most associated with skin cancer development include white race, increased age at transplant, male sex, heart or lung transplant versus kidney or liver transplant, and lower Fitzpatrick phototypes.[2] In our cohort of liver recipients, these traits remained significant predictors of skin cancer development, with the addition of smoking status. Notably, race was a significant risk factor with CART modeling, but not when chi square testing was used. In our sample, the number of non-white liver recipients that met inclusion criteria was small. It is probable that the sample size was not substantial enough for significance with chi square testing.

It is suggested that heart and lung recipient risk for skin cancer is increased due to the aggressive immunotherapies that this type of transplant necessitates.[3] In our liver cohort, the use of cyclosporine in post-transplant regimens was trending toward suggesting that providers may need a lower threshold for referral to dermatology for skin cancer surveillance.

In general, transplant recipients are estimated to be at a 40 – 250 times increased risk for cutaneous SCC and a three-fold increased risk for MM.[3] While liver patients may be at less of a risk for skin cancer development as compared to other transplant types, nearly half of the patients in our cohort developed skin cancer. Like other transplant types, liver recipients are most likely to develop SCC, followed by BCC, and MM. Skin cancers in this cohort are most common on sun exposed areas of the head, neck, and upper extremities.

While no official guidelines for referral for skin cancer surveillance screening post-transplant exist, the consensus in the literature is to refer one-year post-transplant,[2] especially for those patients at high-risk in our cohort, including white race, age >43 years at transplant, current or former smokers, or prescribed CsA. In our cohort of liver recipients, however, skin cancer took longer to develop. Future, larger scale studies in liver recipients are needed to determine the appropriate interval for dermatologic evaluation. Referral stratification may alleviate burden, allowing dermatologic appointments to be given to those most at risk for serious morbidity and mortality.[2] Targeted interventions to educate liver recipients on their risk for skin cancer may also be useful.

Conflict of Interest Disclosures: None

Funding: None

Corresponding Author:
Chelsea Shope, MSCR
135 Rutledge Ave., 11th Floor
Charleston, SC 29425
Phone: (843) 754-9577
Email: shopec@musc.edu

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