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# Long-term incidence and outcomes of skin cancer in kidney transplant recipients under reduced-dose immunosuppression: A retrospective cohort study

Gabriela Orozco [a,1], Julia Andrea Gómez-Montero [b,2], Isabella Monsalve [c,3], Santiago Cabas [b,4], Andrea Garcia-Lopez [b,5,*], Fernando Giron-Luque [b,d,6]

[a] Dermatology Resident, General Polyclinic of Rio de Janeiro, Carlos Chagas Higher Institute of Health Sciences, Rio de Janeiro, Brazil
[b] Department of Research, Colombiana de Trasplantes, Bogotá, Colombia
[c] Faculty of Medicine, Universidad El Rosario, Bogotá, Colombia
[d] Department of Transplant Surgery, Colombiana de Trasplantes, Bogotá, Colombia

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ABSTRACT

*Introduction:* Skin cancer is the most common malignancy in kidney transplant recipients (KTRs), with a higher aggressiveness due to prolonged immunosuppression. Optimizing immunosuppressive regimens may reduce risk while preserving graft function. This study aimed to determine the long-term incidence and characteristics of skin cancer in KTRs receiving steroid-free, reduced-dose calcineurin inhibitor therapy.
*Methods:* We conducted a retrospective cohort study including all KTRs transplanted between 2008 and 2018 at *Colombiana de Trasplantes*. Demographic, clinical, and histopathological data were extracted from institutional records. Patients were stratified by the occurrence of skin cancer. Statistical analyses included descriptive and comparative estimates, Kaplan–Meier survival curves, and log-rank tests.
*Results:* A total of 1660 KTRs were analyzed, with 34 developing skin cancer, yielding a cumulative incidence of 2.05%. Patients with skin cancer were significantly older at transplantation than those without (52.5 ± 10.7 vs. 43.2 ± 13.3 years, $p < 0.001$). No other baseline variables differed between groups. The cumulative risk of skin cancer increased progressively with follow-up: 7.1% at 5 years and 17.8% at 10 years post-transplant.
*Conclusion:* This single-center study is the first in Colombia to describe long-term skin cancer outcomes in kidney transplant recipients (KTRs) under steroid-free, reduced-dose immunosuppression. The incidence observed in this cohort was lower than that reported in international series, which may reflect a potential protective effect of optimized immunosuppressive regimens; however, the possibility of underdiagnosis cannot be excluded. These findings highlight the need for sustained dermatologic surveillance beyond 5 years post-transplant and support strategies to optimize immunosuppressive regimens.

* Corresponding author at: Ave Cra 30 #47a - 74, Cundinamarca, Teusaquillo, Bogotá, Colombia.
*E-mail addresses:* orozcogabriela17@gmail.com (G. Orozco), ja.gomez19@uniandes.edu.co (J.A. Gómez-Montero), isabella.monsalve@urosario.edu.co (I. Monsalve), scabas@colombianadetrasplantes.com (S. Cabas), aegarcia@colombianadetrasplantes.com (A. Garcia-Lopez), fgiron@colombianadetrasplantes.com (F. Giron-Luque).
[1] Contact information: Gabriela Orozco. Address: Av. Gen. Osvaldo Cordeiro de Farias, 466 - Marechal Hermes, Rio de Janeiro - RJ, 21610-480, Brazil, Phone number: 3118540071.
[2] Julia Andrea Gómez-Montero. Address: Ave Cra 30 #47a - 74, Teusaquillo, Bogotá, Cundinamarca, Phone number:3058176395.
[3] Isabella Monsalve. Address: Ak Carrera 24 #63C-69, Barrios Unidos, Bogotá. Phone number: 3108553766.
[4] Santiago Cabas, Address: Ave Cra 30 #47a - 74, Teusaquillo, Bogotá, Cundinamarca. Phone number: 3013219691.
[5] Invoice to: Andrea Garcia-Lopez: Address: Ave Cra 30 #47a - 74, Teusaquillo, Bogotá, Cundinamarca. Phone number: 3005024618.
[6] Fernando Giron-Luque. Address: Ave Cra 30 #47a - 74, Teusaquillo, Bogotá, Cundinamarca. Phone number: 3103467910.

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## Introduction

Skin cancer is the most common type of cancer among kidney transplant recipients (KTRs) and tends to present more aggressively compared to the general population [1,2]. The most frequent types are non-melanoma skin cancers, such as basal cell carcinoma and squamous cell carcinoma [3]. This increased risk can be attributed to the interaction between the immune system and oncogenesis, as prolonged immunosuppression compromises immune surveillance, hindering the elimination of emerging neoplastic cells and facilitating the persistence of oncogenic opportunistic infections [1,4].

For example, previous studies have hypothesized that tacrolimus may elevate TGF-β levels, thereby promoting tumor progression and metastasis. Similarly, it has been suggested that calcineurin inhibitors interfere with NF signaling in activated T cells, which could lead to p53 activation—a key marker in certain non-melanoma skin cancers (NMSC). Cyclosporine has also been proposed to contribute to tumor development through the overexpression of TGF-β and IL-6, as well as by inhibiting DNA repair, facilitating the accumulation of mutations [1]. Likewise, the oncogenic potential of azathioprine has been widely acknowledged, as it is believed to sensitize the skin to UVA radiation and promote the accumulation of 6-thioguanine in DNA, increasing the risk of NMSC [1,4]. However, further studies are needed to confirm the specific mechanisms by which immunosuppressive agents contribute to the development of skin cancer in renal transplant recipients.

Consequently, skin cancer has been recognized as one of the three leading causes of mortality among (KTRs), with an overall risk up to four times higher than in the non-transplanted population [5]. Nevertheless, evidence from Latin America remains scarce. The largest regional cohort to date, conducted in Mexico, reported a prevalence of 6.6% and highlighted the urgent need to better characterize renal transplant patients with cutaneous neoplasms in this setting [6]. In Colombia, a cross-sectional study conducted in Bogotá in 2014 evaluated 85 KTRs who presented with skin lesions and reported a prevalence of malignant skin lesions of 2.4% (2 cases). The affected patients were diagnosed with skin cancer at 2 and 22 months post-transplant, respectively [7]. To date, no studies in the country have estimated the incidence of skin cancer in kidney transplant recipients or provided long-term follow-up data.

Several risk factors for skin cancer have been identified, including heredity, multiple typical or atypical nevi, exposure to arsenic, coal, or ultraviolet light, geographic latitude, repeated exposure to X-rays, burns, advanced age, male sex, prior history of skin cancer, and immunosuppression, among others [8]. With an aging population and longer survival among KTRs, prioritizing preventive strategies in this group becomes essential [9]. Although the impact of immunosuppressive therapies in transplant patients is well documented, few global studies have evaluated specific methods for stratifying skin cancer risk in this population [10]. Even in the United States, evidence remains limited, and standardized recommendations for risk stratification and screening in KTRs are still lacking [11].

Optimizing immunosuppressive regimens is crucial to balance efficacy and safety. Our protocol is based on reduced doses of calcineurin inhibitors and the exclusion of corticosteroids, except in patients with high immunological risk. This strategy seeks to minimize immunosuppressive toxicity, including the oncogenic potential of these agents, while preserving adequate immunoprotective effects.

Given these considerations, local studies are needed to enable early diagnosis and timely treatment of skin cancer in transplant recipients [12]. Although tools for monitoring cutaneous neoplasms have been developed in recent years, further refinement is required to improve their effectiveness and clinical impact [10]. In addition, prevention-oriented strategies may help reduce healthcare costs, as immunosuppressed patients face a higher risk of developing metastases [13,14].

The objective of this study is to estimate the cumulative incidence of skin cancer and to describe the clinical, sociodemographic, and histopathological characteristics of KTRs receiving optimized immunosuppressive therapy with reduced doses of calcineurin inhibitors in a corticosteroid-free regimen.

## Methods

### *Study design*

We conducted an observational, analytical, retrospective cohort study based on a review of medical records of kidney transplant recipients (KTRs) treated at Colombiana de Trasplantes. The study included transplants performed from August 2008 to August 2018, with patient follow-up available through August 2023. Data were collected from August 2023 to February 2024, and all analyses were completed by June 2024. Clinical characteristics and risk factors were compared between patients with and without a diagnosis of skin cancer.

### *Population and sample*

The study included adult patients with a history of a first kidney transplant performed at our center. Colombiana de Trasplantes carries out approximately 20% of the country's transplant procedures and operates in four cities across Colombia, following standardized management guidelines and maintaining detailed and uniform records on immunosuppressive protocols.

### *Immunosuppression protocols*

All patients received standard induction therapy with alemtuzumab, basiliximab, or anti-thymocyte globulin, depending on immunological risk or clinical transplant guidelines. Our long-term immunosuppressive regimen is steroid-free, and steroids are only administered to patients with high immunological risk. Of note, this protocol is defined by the implementation of a reduced-dose regimen of calcineurin inhibitors, a strategy aimed at minimizing drug-related toxicity while maintaining effective immunosuppression.

Therapeutic changes in immunosuppression were assessed by comparing the doses of each immunosuppressive agent before and after the diagnosis of cancer.

Baseline immunosuppression was defined using the treatment regimen recorded during the 1 to 30 days before biopsy-confirmed diagnosis. For this baseline assessment, we extracted the type of mycophenolate formulation, mycophenolate dose normalized to body surface area (mg/m$^2$, twice daily), tacrolimus total daily dose (mg/day), tacrolimus weight-based dose (mg/kg/day), and tacrolimus trough blood levels (ng/mL). Suboptimal tacrolimus exposure was predefined as a trough level $<5$ ng/mL. We also identified patients receiving mycophenolate doses $>600$ mg/m$^2$ twice daily and tacrolimus doses $<0.01$ mg/kg/day.

Changes in immunosuppression after diagnosis were assessed at the first outpatient follow-up visit after the biopsy result had been documented in the medical record. Because patients in our program are routinely seen monthly, this post-diagnosis assessment reflects treatment modifications implemented at the visit immediately following histopathologic confirmation, typically within approximately one month after diagnosis. Immunosuppression changes were classified as any documented dose reduction, treatment discontinuation, or immunosuppressant exchange. Dose reductions were further categorized as $<50\%$ or $\geq 50\%$ relative to the pre-diagnosis regimen.

### *Case definition and identification*

A list of keywords aligned with the study objectives was first developed, including suggestive terms associated with skin cancer as well as the corresponding ICD-10 diagnostic codes. Based on this, a

manual review of medical records from kidney transplant patients at *Colombiana de Trasplantes* was conducted for the follow-up period between 2008 and 2018. To be eligible, patients were required to have a minimum of five years of post-transplant follow-up. The review aimed to document lesion development, immunosuppressive regimens, and histopathological findings. All cases of skin cancer were diagnosed by biopsy, confirming either basal cell carcinoma or squamous cell carcinoma. However, in a small subset of patients, the complete histopathological report was not available in the medical records, which limited the level of detail for subsequent analysis.

Ultraviolet (UV) exposure level was classified according to categories established in a document published by the World Health Organization (WHO) in collaboration with other institutions for Colombia. The classification considered the city of origin of each patient and was categorized into four levels: moderate, moderate–high, high, and very high. This variable was included to evaluate the potential influence of geographic UV radiation on the development of skin cancer in KTRs [15].

### *Statistical analysis*

The study population was described using measures of central tendency and dispersion for continuous variables and proportions for categorical variables. Group comparisons were performed with chi-square tests for categorical variables and Student's *t*-tests or non-parametric tests, depending on data distribution, for continuous variables. A two-sided $p$-value $<0.05$ was considered statistically significant. The cumulative incidence of skin cancer at 5, 10, and 15 years post-transplant was calculated and expressed as a percentage. Additionally, the cumulative probability of developing skin cancer over time was estimated using Kaplan–Meier risk curves. All statistical analyses were conducted with R software, version 4.3.3 [16].

### *Ethical considerations*

This study was conducted in compliance with national and international regulations on health research, including the principles of the Declaration of Helsinki and Colombia's Resolution 8430 of 1993 [17, 18]. As it was a retrospective study based on secondary data, it was classified as research without risk according to the Colombian regulations. The Research Ethics Committee reviewed and approved the protocol, granting a waiver of informed consent.

## Results

### *Characterization of transplant patients*

Between 2008 and 2018, a total of 1660 kidney transplant recipients were analyzed, of whom 34 developed skin cancer, corresponding to a cumulative incidence of 2.05%. In the overall cohort, the maximum follow-up was 15.96 years, with a median follow-up of 3.48 years (IQR, 1.05–6.52 years). During follow-up, 413 patients experienced graft loss and 262 died. Among patients who developed skin cancer, the median time from transplantation to cancer diagnosis was 6.21 years (IQR, 4.99–7.94 years). Among the variables evaluated, age at the time of skin cancer diagnosis showed the largest difference between groups (43.2 ± 13.3 vs. 52.5 ± 10.7 years), a difference that was statistically significant (Table 1).

A higher proportion of male patients was observed in both groups; however, the difference was not statistically significant, suggesting that sex is not a determining factor in the development of skin cancer among transplant recipients. With respect to place of residence, only a small percentage of patients were from rural areas, and no significant differences were identified between groups. Although not statistically significant, a greater proportion of patients with a history of smoking was found among those who developed skin cancer, which may reflect a higher prevalence of this habit in affected recipients. Finally, differences in donor type and etiology of kidney disease were observed between groups, but these did not reach statistical significance.

**Table 1**
Clinical and sociodemographic characteristics of KTRs with and without a diagnosis of skin cancer between 2008 and 2018.

| | No cancer (N = 1626) | Skin cancer (N = 34) | Total (N = 1660) | P value |
|---|---|---|---|---|
| Age at transplant (years) | | | | |
| Mean (SD) | 43.2 (13.3) | 52.5 (10.7) | 43.4 (13.3) | <0.001 |
| Median [Min, Max] | 43.0 [18.0, 77.0] | 52.0 [25.0, 70.0] | 43.0 [18.0, 77.0] | |
| Gender | | | | |
| Female | 663 (40.8%) | 13 (38.2%) | 676 (40.7%) | 0.956 |
| Male | 963 (59.2%) | 21 (61.8%) | 984 (59.3%) | |
| Area | | | | |
| Rural | 119 (7.3%) | 2 (5.9%) | 121 (7.3%) | 0.95 |
| Urban | 1507 (92.7%) | 32 (94.1%) | 1539 (92.7%) | |
| Smoker | 502 (30.9%) | 15 (44.1%) | 517 (31.1%) | 0.256 |
| CKD etiology | | | | |
| Congenital | 15 (0.9%) | 0 (0%) | 15 (0.9%) | 1 |
| Unknown | 780 (48.0%) | 13 (38.2%) | 793 (47.8%) | |
| Diabetes | 210 (12.9%) | 5 (14.7%) | 215 (13.0%) | |
| Glomerular | 324 (19.9%) | 5 (14.7%) | 329 (19.8%) | |
| High blood pressure | 180 (11.1%) | 4 (11.8%) | 184 (11.1%) | |
| Obstructive | 45 (2.8%) | 1 (2.9%) | 46 (2.8%) | |
| Other | 56 (3.4%) | 1 (2.9%) | 57 (3.4%) | |
| Donor type | | | | |
| Deceased | 1104 (67.9%) | 25 (73.5%) | 1129 (68.0%) | 0.784 |
| Living | 522 (32.1%) | 9 (26.5%) | 531 (32.0%) | |
| History of Diabetes | 273 (16.8%) | 7 (20.6%) | 280 (16.9%) | 0.843 |

SD: Standard deviation. CKD: Chronic Kidney Disease. PMH: Past medical history. Missing values CKD etiology 21 (1.3%).

### *Clinical and histopathological characteristics of skin cancer in transplant patients*

Cases were diagnosed between 6 months and 14 years post-transplant, with a median follow-up of 6.2 years. All skin cancer diagnoses were confirmed by biopsy, with both basal cell carcinoma and squamous cell carcinoma evenly distributed within the sample. More than half of the tumors exhibited invasive features, and lesions were predominantly located in the cephalic region. Most patients underwent surgical resection, and only one case (2.9%) experienced recurrence. In a few patients the complete histopathological report was not available in the medical records (Table 2). Notably, no cancer-related mortality was observed during the study period.

### *Immunosuppressive regimens and modifications after skin cancer diagnosis*

Regarding baseline immunosuppression before biopsy-confirmed diagnosis, mycophenolate was the most frequently used agent (30/34, 88.2%), followed by tacrolimus (26/34, 76.4%), sirolimus (5/34, 14.7%), cyclosporine (Cyclosporine capsules), and azathioprine and everolimus (1/34 each, 2.9%). Among patients receiving mycophenolate, 15 were treated with mycophenolate mofetil and 15 with mycophenolic acid; the median dose per $m^2$ twice daily was 295 [166, 391] for mycophenolate mofetil and 209 [125, 281] for mycophenolic acid, and no patient received doses >600 mg/$m^2$ twice daily. Among tacrolimus-treated patients, the median dose was 4 mg/day [0, 8] and 0.052 mg/kg/day [0.01, 0.16], with no patient receiving <0.01 mg/kg/day. Median tacrolimus trough level before diagnosis was 5.75 ng/mL [2.8, 12.5], and 7/26 patients (26.9%) had suboptimal levels (<5 ng/mL). After diagnosis, 20/34 patients (58.8%) underwent at least one immunosuppression change. Tacrolimus was discontinued in 1/26 patients (3.8%), reduced by <50% in 9/26 (34.6%), and reduced by ≥50% in 1/26 (3.8%). Mycophenolate was reduced by <50% in 4/30 patients

**Table 2**
Clinical and histopathological characterization of transplant patients diagnosed with skin cancer between 2008 and 2018.

| Characteristic (n, %) | Total (n = 34) |
|---|---|
| Type of skin cancer | |
| Basal cell carcinoma | 17 (50.0%) |
| Squamous cell carcinoma | 17 (50.0%) |
| Years since transplant at diagnosis | |
| Mean (SD) | 6.70 (3.42) |
| Median [Min, Max] | 6.21 [0.570, 14.0] |
| Unknow | 3 (8.8%) |
| UV exposure level | |
| Moderate | 3 (8.8%) |
| Moderate - High | 4 (11.8%) |
| High | 2 (5.8%) |
| Very high | 25 (73.5%) |
| Changes in the characteristics of the lesion | |
| Yes | 5 (14.7%) |
| No | 2 (5.9%) |
| Unknown | 27 (79.4%) |
| Biopsy diagnosis | |
| Yes | 27 (79.4%) |
| Unknown | 7 (20.6%) |
| Invasion | |
| Dermis reticular | 9 (26.4%) |
| In situ | 5 (14.7%) |
| Unspecified infiltrating | 4 (11.7%) |
| Unknown | 16 (47.1%) |
| Number of lesions | |
| Single | 17 (50.0%) |
| Multiple | 16 (47.1%) |
| Unknown | 1 (2.9%) |
| Location | |
| Cephalic | 24 (70.6%) |
| Cephalic + Extracephalic | 4 (11.8%) |
| Extracephalic | 4 (11.8%) |
| Unknown | 2 (5.9%) |
| Management modifications | 20 (58.8%) |
| Outcome | |
| Not resected | 2 (5.9%) |
| Recurrence | 1 (2.9%) |
| Completely resected | 7 (20.6%) |
| Partially resected | 4 (11.8%) |
| Resection without margin information | 10 (29.4%) |
| Unknown | 10 (29.4%) |

SD: Standard deviation.

**Table 3**
Immunosuppression before and after the diagnosis of skin cancer in transplant patients between 2008 and 2018.

| Baseline immunosuppression before biopsy-confirmed diagnosis | Total (n = 34) |
|---|---|
| Immunosuppressive drugs, n (%) | |
| Mycophenolate | 30 (88.2%) |
| Tacrolimus | 26 (76.4%) |
| Cyclosporine | 2 (5.8%) |
| Azathioprine | 1 (2.9%) |
| Sirolimus | 5 (14.7%) |
| Everolimus | 1 (2.9%) |
| Drug-specific regimen details | |
| Mycophenolate | |
| Formulation, n (%) | |
| mycophenolate mofetil (CellCept) | 15 (44.1%) |
| Mycophenolic acid (MPA) | 15 (44.1%) |
| Dose per $m^2$ BID, median [min, max] | |
| mycophenolate mofetil (CellCept) | 295 [166,391] |
| Mycophenolic acid (MPA) | 209 [125, 281] |
| Patients with dose >600 mg/$m^2$ BID, n (%) | 0 (0.0) |
| Tacrolimus | |
| Dose, mg/day, median [min, max] | 4 [0, 8] |
| Dose, mg/kg/day, median [min, max] | 0.052 [0.01, 0.16] |
| Patients with dose <0.01 mg/kg/day, n (%) | 0 (0.0) |
| Trough level, ng/mL, median [min, max] | 5.75 [2.8, 12.5] |
| Patients with trough <5 ng/mL, n/N (%) | 7/26 (26.9%) |
| Cyclosporine, dose, mg/day, median [min, max] | 100 [100, 100] |
| Azathioprine, dose, mg/day | 100 |
| Sirolimus, dose, mg/day, median [min, max] | 2 [1,4] |
| Everolimus, dose, mg/day | 3 |
| Immunosuppression changes after diagnosis | |
| Any change in immunosuppression, n (%) | 20 (58.8%) |
| Dose reduction or discontinuation, n/N (%) | |
| Tacrolimus discontinued | 1/26 (3.8%) |
| Tacrolimus reduced <50% | 9/26 (34.6%) |
| Tacrolimus reduced ≥50% | 1/26 (3.8%) |
| Mycophenolate reduced <50% | 4/30 (13.3%) |
| Mycophenolate reduced ≥50% | 2/30 (6.6%) |
| Everolimus reduced ≥50% | 1/1 (100%) |
| Cyclosporine reduced <50% | 2/2 (100%) |
| Azathioprine reduced ≥50% | 1/1 (100%) |
| Sirolimus reduced ≥50% | 2/5 (40%) |
| Immunosuppressive drug switches, n/N (%) | |
| Tacrolimus to everolimus | 2/26 (7.2%) |
| Mycophenolate to everolimus | 1/30 (3.3%) |

Baseline immunosuppression was assessed using the regimen recorded within 1–30 days before biopsy-confirmed diagnosis. Post-diagnosis changes were assessed at the first outpatient visit after the biopsy result was documented in the medical record. Because patients are routinely followed monthly, this time point generally reflects treatment modifications made within approximately 1 month after diagnosis. Percentages in the baseline drug section were calculated using the full cohort (n = 34). Percentages for drug-specific changes were calculated using the number of patients receiving each drug at baseline. Categories of post-diagnosis changes were not mutually exclusive.

(13.3%) and by ≥50% in 2/30 (6.6%). Everolimus was reduced by ≥50% in 1/1 patient (100.0%), cyclosporine was reduced by <50% in 2/2 (100.0%), azathioprine was reduced by ≥50% in 1/1 (100.0%), and sirolimus was reduced by ≥50% in 2/5 (40.0%). Drug switches were uncommon and included tacrolimus to everolimus in 2/26 patients (7.2%) and mycophenolate to everolimus in 1/30 (3.3%) (Table 3).

With respect to induction therapy, alemtuzumab was the most frequently used agent, administered in 47% of patients, and was the predominant choice until 2011. From 2011 onwards, rabbit antithymocyte globulin became the most commonly employed induction agent (44.1%), while basiliximab was used in only 8.8% of cases. No patient was using corticosteroids such as prednisolone or deflazacort. Similarly, acute graft rejection occurred in 14% of cases.

### *Clinical course and outcomes of patients with skin cancer*

During the follow-up of kidney transplant recipients, the median time from transplantation to cancer diagnosis was 6.21 years. Among these cases, the date of skin cancer diagnosis was unknown in three patients, while three others were diagnosed nearly 14 years post-transplant. Fig. 1 shows the outcome recorded for each case: five patients (14.7%) experienced graft loss, and acute graft rejection was recorded in five patients (14.7%), although these were not the same five individuals. Specifically, graft loss occurred in cases 3, 5, 13, 15, and 18, whereas acute graft rejection was recorded in cases 3, 5, 13, 14, and 28; only three patients overlapped (cases 3, 5, and 13). Based on the available data, graft loss events could not be attributed solely to immunosuppression reduction or skin cancer treatment. Additionally, changes in immunosuppressive medications were made in 20 patients (58.8%). Lesion resection was performed in 21 patients (61.7%). Only one patient had a recurrence, representing 2.9%.

### *Cumulative risk of skin cancer over time post-transplant*

Fig. 2 shows the cumulative probability of developing skin cancer among KTRs over time. At 5 years post-transplant, the risk is approximately 1.1%, increasing to 7.1% at 10 years and reaching nearly 17.8% at 15 years. A marked acceleration in risk is observed after the first decade, highlighting the growing cumulative probability of skin cancer in this population, particularly in the long term.

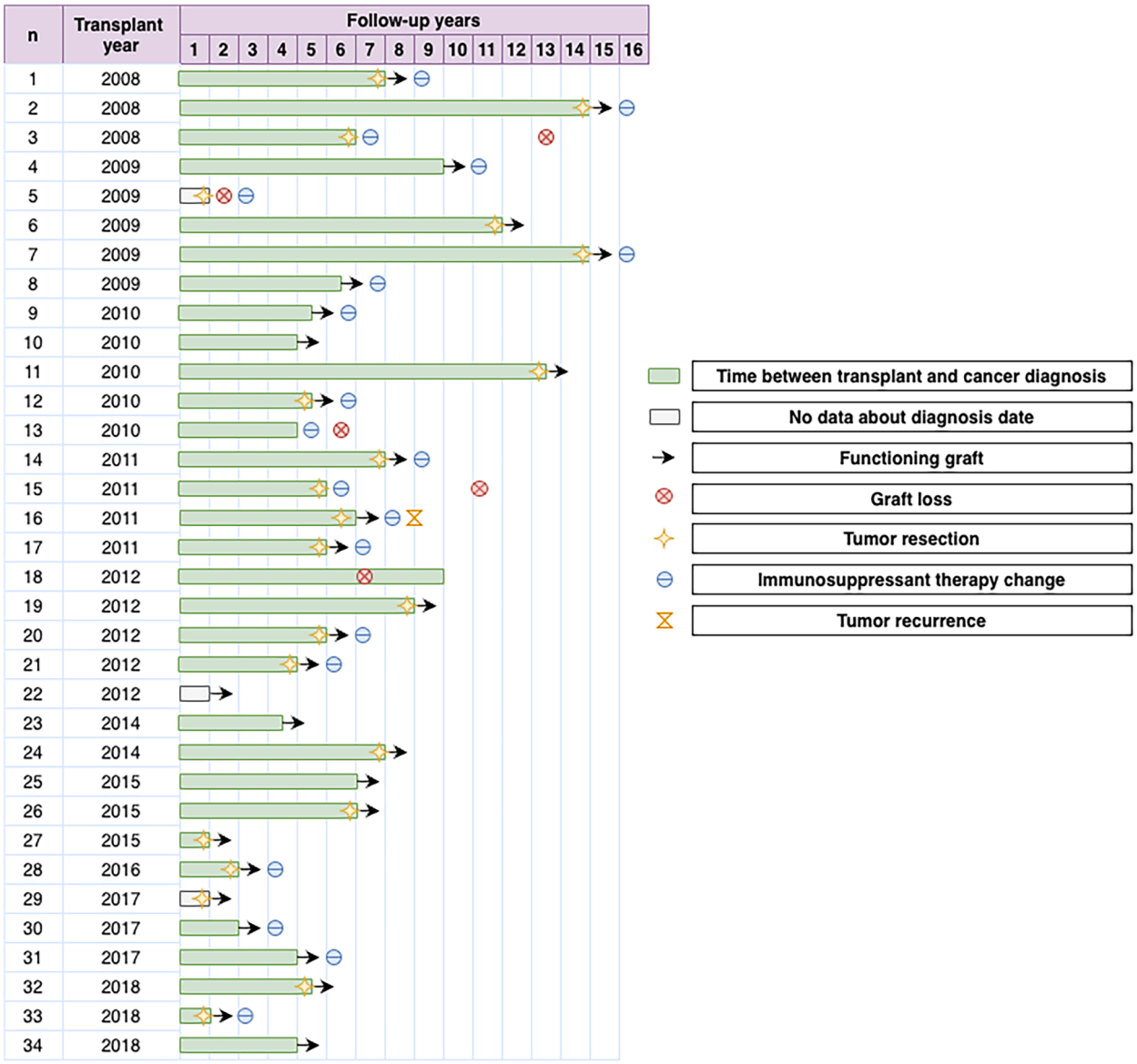


**Fig. 1.** Follow-up from kidney transplantation to skin cancer diagnosis among kidney transplant recipients transplanted between 2008 and 2018.

## Discussion

This is the first study in Colombia to characterize the development of skin cancer in KTRs managed with a steroid-free immunosuppressive regimen. At our center, the cumulative incidence of skin cancer was relatively low (2.05%), which may be associated with the use of steroid-free regimens and the optimized administration of reduced doses of calcineurin inhibitors. However, a progressive increase in risk was evident with longer post-transplant follow-up, particularly after 5 years (7.1%) and 10 years (17.8%). Patients who developed skin cancer were also older at the time of transplantation compared with those without a diagnosis of cutaneous neoplasia (52.5 ± 10.7 vs. 43.2 ± 13.3 years, $p < 0.05$). These findings underscore the importance of long-term dermatologic surveillance in this population and the need for targeted strategies to prevent neoplastic skin complications.

### *Comparison of incidence with previous studies*

The reported incidence of skin cancer among transplant recipients varies widely depending on the characteristics of each population. One of the highest incidences was documented in Australia, where 45% of patients developed skin cancer within 10 years post-transplantation [9]. In the United States, the 10-year risk ranges between 11% and 35% [19] Regionally, a study in Brazil reported a prevalence of 17% during the first year after transplantation [20]. Given that Brazil is a country with high ultraviolet radiation exposure, this factor may contribute to an increased risk of skin cancer among transplant [20,21].

In Colombia, a previous study conducted in Bogotá in 2014 reported a one-year prevalence of 2.4% [7]. In contrast, the present study analyzed patients transplanted over a 10-year period, with follow-up extending up to 15 years, and found a cumulative incidence of 2.05%. It is important to note that these are different epidemiological indicators and therefore cannot be directly compared. However, this and several previous studies consistently show a lower presence of skin cancer in our population.

Additionally, some authors have highlighted that skin cancer is more common among individuals with lighter phototypes [9,22,23]. Considering that our study population is predominantly mestizo, this demographic characteristic may act as a potential confounding factor and partially explain the lower incidence observed.

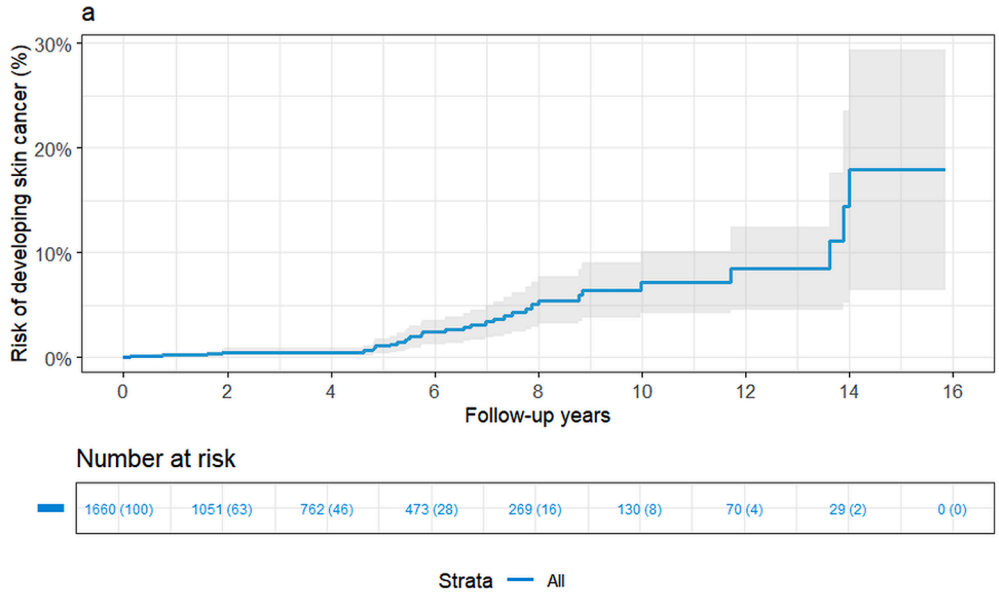


**Fig. 2.** Cumulative probability of skin cancer in kidney transplant patients between 2008 and 2018.

*Post-transplant time analysis and cumulative risk*

The increased long-term risk may be attributed to chronic ultraviolet (UV) radiation exposure and sustained immunosuppression, which are consequences of improved survival in transplant patients due to advances in therapeutic management. Previous studies have reported that 1 in 2 transplant recipients do not practice adequate daily photoprotection. Additionally, countries with high UV radiation levels are associated with a higher risk of skin cancer. However, a systematic review suggests that UV exposure may not be a significant risk factor for melanoma in individuals with skin color other than white, highlighting the need to consider other factors [24]. Moreover, prior research shows that older age groups tend to experience higher levels of sun exposure [21]. In the context of the present study, this suggests that other factors—such as the predominant phototype in our population or the immunosuppressive approach used—may be modulating the risk of skin cancer in our transplant patients.

Regarding the time between transplantation and the diagnosis of skin cancer, a study conducted in Mexico found that patients developed skin cancer after approximately 6.5 years [25]. This is slightly shorter compared to the findings of the present study, where the average was 6.7 years. Again, this difference may be attributed to the use of a steroids-free therapy, as well as the ongoing monitoring and optimization of all immunosuppressive agents at reduced doses. In fact, the same study demonstrated that adding an additional immunosuppressive drug to the treatment regimen reduced the time to disease onset [25]. Therefore, it is possible that the immunosuppressive optimization strategy applied at our center slightly delays the onset of skin cancer in transplanted patients.

The findings of this study suggest that older age at the time of transplantation may play a key role in the pathogenesis of skin cancer among kidney transplant recipients. This hypothesis aligns with previous studies that have reported a higher incidence of cutaneous neoplasms in older transplant patients [22], attributing it to cumulative actinic damage, reduced DNA repair capacity, and progressive immunosenescence [9]. In this context, it is plausible that the interaction between these factors and prolonged immunosuppression promotes the proliferation of malignant cells while diminishing the immune system's ability to eliminate them efficiently [4,26]. Another important feature in transplant recipients is that they tend to develop the disease earlier than the general population [27]. Our findings support this association and highlight the need to assess age-specific dermatological follow-up strategies at the time of transplantation, thereby optimizing early detection and management of these neoplasms in this high-risk population [14, 28].

*Role of immunosuppression and potential clinical implications*

Skin cancer screening in solid organ transplant recipients is a practice recommended by various clinical guidelines, with suggestions for annual evaluation and, in some cases, risk stratification [14]. However, these guidelines are based on populations with characteristics different from ours and do not consider factors such as skin phototype, ultraviolet radiation exposure, and photoprotection habits, all of which influence the incidence and presentation of skin cancer. Given this variability, relying solely on international guidelines may be insufficient, underscoring the need to generate local evidence to adapt screening and prevention strategies to our population. In fact, some recommendations are based more on expert opinion than on standardized studies [1]. For example, kidney transplant recipients from incompatible living donors present a higher risk due to the greater need for initial immunosuppression and its impact on oncogenic pathways [29]. This highlights the need for management guidelines that personalize risk based on patient-specific characteristics, optimizing immunosuppression and improving clinical outcomes.

Reduction of immunosuppression has been reported as an effective therapeutic strategy for transplant-associated skin cancer [30]. However, decreasing immunosuppressive therapy may also increase the risk of organ rejection, which means the potential risks and benefits of this strategy must be carefully assessed in collaboration with transplant specialists and under close clinical monitoring [14,28]. This remains one of the main concerns for the clinical team, as it involves a delicate balance between oncological control and preservation of graft function. Furthermore, each immunosuppressive agent appears to act through distinct molecular mechanisms in promoting carcinogenesis, with the associated risk also seeming to be modulated by treatment dosage [26].

In multiple populations, the pivotal role of immunosuppressive therapy in increasing the risk of all types of cancer has been well documented [1,23]. Specifically, the standardized incidence ratio is elevated by 65 to 250 times for squamous cell carcinoma (SCC), up to 16 times for basal cell carcinoma (BCC), and up to 8 times for melanoma (MM) [9,23,28]. Although the general evidence indicates that the

duration of immunosuppression increases the risk of skin cancer [9], some studies have shown that exposure to immunosuppressive agents for more than five years may lead to a heightened risk beyond that period [7]. In our cohort, the most common immunosuppressive regimen included calcineurin inhibitors and mycophenolate, with adjustments made after diagnosis in 58.8% of cases. Additionally, 7 out of 26 tacrolimus-treated patients (26.9%) had suboptimal tacrolimus trough levels (<5 ng/mL) at the time of diagnosis, prior to any immunosuppression adjustment.

In our cohort, immunosuppression was primarily based on mycophenolate and tacrolimus, with adjustments made in 58.8% of patients. Dose reductions were the most common type of modification, particularly for tacrolimus (34.6% reduced by <50% and 3.8% reduced by ≥50%) and mycophenolate (13.3% reduced by <50% and 6.6% reduced by ≥50%). Drug switches were uncommon and included tacrolimus to everolimus in 2/26 patients (7.2%) and mycophenolate to everolimus in 1/30 (3.3%), in cases where the oncological benefit of mTOR inhibition was the primary indication. This aligns with the literature, which suggests that these agents may reduce the risk of secondary neoplasms, although their impact on skin cancer prevention is not yet fully established [31,32]. Furthermore, since no patients received corticosteroids, their potential contribution to increased skin cancer risk, as suggested in the literature [23], was avoided. Likewise, the optimized immunosuppression strategy appears to preserve graft function, with only 14.7% of cases experiencing rejection, most of which occurred after five years post-transplant. Moreover, surgical excision is the main treatment for skin cancer in transplant patients, alongside immunosuppression management [28,33]. New systemic therapies like immune checkpoint inhibitors show promise for advanced cases [34].

Regarding dermatological surveillance, given the relatively low incidence of skin cancer observed in our population, routine annual dermatological screening was not performed for all kidney transplant recipients. Instead, referral to dermatology was reserved for patients considered to be at higher risk, based on clinical criteria such as prolonged immunosuppression, history of significant sun exposure, fair skin phototype, or prior skin lesions. We acknowledge that this risk-based approach, compared to universal annual screening as recommended by guidelines such as KDIGO 2009, may result in underdetection of early skin cancers and pre-cancerous lesions in lower-risk patients. Additionally, retinoids (vitamin A derivatives), including acitretin, were not used for skin cancer chemoprevention in any patient in our cohort during the study period (2008–2018).

### *Limitations*

This study has several limitations that should be considered when interpreting the results. First, its retrospective design may be subject to information bias due to the quality and availability of medical records. Second, the sample was obtained from a single referral center, which may limit the external validity of the findings. Additionally, relevant variables such as skin phototype, cumulative ultraviolet radiation exposure, and photoprotection practices were not included in the analyses—factors that have been identified as key determinants in the development of cutaneous neoplasms among immunosuppressed populations. The absence of these data limits the ability to more accurately assess their impact on the incidence of skin cancer in our cohort. Therefore, the need for prospective and multicenter studies is emphasized, to allow for a more detailed and precise evaluation of risk factors and prevention strategies in this population.

## Conclusion

Our findings highlight a lower cumulative incidence of skin cancer in KTRs compared to international reports, which may be influenced by the immunosuppressive regimen used as well as the clinical and demographic profile of the population. We believe these results may be useful for optimizing immunosuppressive management, guiding dermatological surveillance, and supporting the development of clinical guidelines tailored to our population. However, the progressive increase in risk over time post-transplant underscores the importance of establishing long-term dermatological monitoring strategies and individualized approaches to immunosuppression modulation. Prospective and multicenter studies are needed to validate these findings and strengthen recommendations for skin cancer screening and prevention among transplant patients in Colombia.

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## CRediT authorship contribution statement

**Gabriela Orozco:** Conceptualization, Methodology, Investigation, Formal analysis, Writing – original draft. **Julia Andrea Gómez-Montero:** Conceptualization, Methodology, Investigation, Formal analysis, Writing – original draft, Writing – review & editing. **Isabella Monsalve:** Investigation, Formal analysis, Writing – review & editing. **Santiago Cabas:** Formal analysis, Writing – original draft, Writing – review & editing, Supervision. **Andrea Garcia-Lopez:** Conceptualization, Methodology, Data curation, Formal analysis, Supervision, Writing – original draft, Writing – review & editing. **Fernando Giron-Luque:** Supervision, Writing – review & editing.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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