External Validation of the SUNTRAC Skin Cancer Prediction tool in a Large European Solid Organ Transplant Recipient Cohort

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KEY POINTS

QUESTION: Is the SUNTRAC (Skin and Ultraviolet Neoplasia Transplant Risk Assessment Calculator) tool valid for guiding skin cancer screening in solid organ transplant recipients (SOTR)?

FINDINGS: In this external validation we found good prognostic discrimination in a European cohort of 3421 SOTR. The observed skin cancer incidences were similar to those predicted from the US SOTR population for each risk group.

MEANING: The SUNTRAC tool can be transported to different populations allowing to stratify SOTR into distinct skin cancer risk groups and identify those at a very high-risk opening the door to efficient and effective preventive measures.

TWEET (255/257 chars)

The SUNTRAC tool can be used in different populations to stratify solid organ transplant patients into distinct skin cancer risk groups to identify high-risk patients, this tool could lead to more effective preventive measures #transplantation #skincancer

ABSTRACT

Importance: The SUNTRAC (Skin and Ultraviolet Neoplasia Transplant Risk Assessment Calculator) tool has been developed in the US to facilitate the identification of solid organ transplant recipients (SOTR) at a higher risk of developing skin cancer. However, it has not yet been validated in populations other than the one used for its creation.

Objective: To provide an external validation of the SUNTRAC tool in different SOTR populations.

Design: Retrospective external validation study on a prospectively collected cohort of European SOTR from the Netherlands (1995-2016) and Spain (2011-2021).

Setting: Two transplant centers at teaching hospitals in the Netherlands and Spain.

Participants: 3421 SOTR that were screened and followed-up at Dermatology departments.

Main Outcome and Measures: We assessed discrimination via a competing risk survival analysis, cumulative incidence plots and Wolbers' concordance index. Calibration was assessed through comparison of predicted skin cancer incidences. Skin cancer diagnoses comprised squamous cell carcinoma, basal cell carcinoma, melanoma, and Merkel cell carcinoma.

Results: 603 patients developed skin cancer out of 3421 SOTR (median age at transplant, 53 years; 2132 [62.3%] male; 2828 [82.7%] white race; 23213 years of contributed follow-up time). The SUNTRAC tool classified patients into four groups with significantly different risks of developing skin cancer during follow-up. Overall, the relative rate for developing skin cancer, estimated using subdistribution hazard ratios, compared to the "Low risk" group was 6.8 for the Medium-risk group ([95% CI, 3.8 - 12], p <0.001), 15.9 for the High-risk group ([95% CI, 8.9 - 28], p <0.001) and 54.8 for the Very-high-risk group ([95% CI, 29 - 103], p <0.001), with a concordance index of 0.72. Skin cancer incidences were similar to those predicted by the SUNTRAC tool.

Conclusions and relevance: Our results support the use of the SUNTRAC tool in European populations for stratifying patients based on their skin cancer risk and also detecting patients at a high-risk of developing skin cancer. This can be helpful in prioritizing and providing better screening and surveillance for these patients.

INTRODUCTION

Between 14 to 37.5% of solid organ transplant recipients (SOTR) will develop skin cancer within 10 years of transplantation.(Colegio & Billingsley, 2011) Among skin malignancies cutaneous squamous cell carcinoma (cSCC), basal cell carcinoma (BCC), melanoma and Merkel cell carcinoma (MCC) are the most frequent. cSCC is often the most concerning due to its higher incidence and aggressive behavior in the SOTR population. cSCC can grow rapidly and metastasize, leading to immunosuppression regime changes that may compromise graft survival, mutilating surgeries, or even the patient's death.

Prevention and early detection are key factors to improve outcomes associated to these tumors.(Crow et al., 2019; Gjersvik, 2019) A recent expert consensus guideline recommends that dermatological screening should be carried out at different times depending on the estimated skin cancer risk of the target population and that risk assessment should be performed with the aid of an evidence-based risk stratification tool.(Crow et al., 2019)

Several skin cancer risk stratification instruments have been developed for the SOTR population.(Carroll et al., 2003; Lowenstein et al., 2017; Urwin et al., 2009) These scores had common variables such as age, race or skin phototype but none was widely used or had large population based studies backing their validity or usability.(Lowenstein et al., 2017)

In 2019, Jambusaria-Pahlajani *et al.* proposed the Skin and Ultraviolet Neoplasia Transplant Risk Assessment Calculator (SUNTRAC) as an easy-to-use screening tool to stratify SOTR according to their skin cancer risk.(Jambusaria-Pahlajani et al., 2019) This tool considers five variables: sex, race, age at transplantation, pretransplant history of skin cancer and type of transplant, these had been identified as risk factors in a large US-based multicenter study.(Garrett et al., 2017) The SUNTRAC tool uses an additive scoring system that classifies patients into four risk groups achieving good prognostic discrimination in the Transplant Skin Cancer Network (TSCN) population study. The authors of the SUNTRAC tool recommend, based on results from a Delphi consensus guideline, optimal screening times for each risk group. (Crow et al., 2019; Jambusaria-Pahlajani et al., 2019) However, external validation in an independent population is often considered an essential pre-requisite for a screening tool before entering clinical practice.(Mallett et al., 2010; Royston & Altman, 2013) To our knowledge, there are no other published studies evaluating the validity of the SUNTRAC screening tool in an independent sample. We present the results of an external validation study evaluating the performance of the SUNTRAC tool in a large European SOTR cohort.

PATIENTS & METHODS

Study populations

We assessed the transportability of the SUNTRAC tool in a diverse European population; two countries with significantly different latitudes and well-known differences in skin cancer incidences were selected to create our European validation cohort.(Ferrándiz & José Fuente, 2001) We included retrospective data from 3654 patients from two ongoing cohorts of SOTR from the Netherlands and Spain. The Dutch cohort is comprised of 2599 patients that received a kidney or pancreatic transplant between 1995 and 2016 while the Spanish cohort is comprised of 1055 patients that received different types of solid organ grafts (i.e., lung, kidney, liver, or heart) between 2011 and 2021. Data were derived from university hospitals carrying out dermatological screening visits and follow-ups of SOTR in Leiden (52°10'N 4°29'E), The Netherlands and Barcelona (41°23'N 2°11'E), Spain. Information was registered prospectively at the time of transplantation and during follow-up visits. CFP in Spain and JBB in the Netherlands coded the race/ethnicity of the patients after asking for their country of origin and ethnic origin during clinical interview and after clinical examination for their skin phototype and phenotypic traits. Multiracial patients were classified under groups different from white race. First skin cancer event after transplant diagnoses were based on histopathological diagnosis of cSCC, BCC, MCC or melanoma by board-certified pathologists. Both databases were approved by the respective hospital ethics committees. As the SUNTRAC tool was intended for the adult SOTR population, pediatric cases were omitted as well as those cases with missing information to compute their SUNTRAC score or missing date of skin cancer diagnosis.

Regarding the reference or derivation cohort, i.e., the population used to generate the SUNTRAC tool, was comprised of 6340 patients from the TSCN multicenter study across 26 centers in the USA with a median latitude of 40°N. These patients received a solid organ transplant either in 2003 or 2008. Most of them were men (63.8%), white race (69.4%), had a median age at transplant of 53 years and 52.3% had received a kidney transplantation. The skin cancer outcome for this cohort included the diagnosis of the first cSCC (91.3%), first melanoma (8.5%) or first MCC (0.2%) but did not consider BCC as a skin cancer outcome. Further details on the derivation cohort can be found elsewhere.(Garrett et al., 2017, 2018; Jambusaria-Pahlajani et al., 2019)

Statistical analysis

Descriptive statistics were computed as customary.(Daniel, 2008) If variables were non-parametric, non-parametric tests were used. We calculated bivariate comparisons by different clinical and demographic characteristics and by SUNTRAC group. To assess statistically significant differences for quantitative variables the Kruskal-Wallis rank sum test was used. Fisher's exact test was used to ascertain differences in proportions.

SUNTRAC scores were computed at the time of transplant and risk groups were assigned as specified by Jambusaria *et al.* (Jambusaria-Pahlajani et al., 2019). SUNTRAC scores were calculated using the original scoring (white race = 9 points, pre-transplant history of skin cancer = 6 points, age ≥ 50 years = 4 points, male sex = 2 points, thoracic organ transplant (heart or lung) = 1 point). We then assigned the patients to their corresponding risk group depending on their total SUNTRAC score at the time of transplant (Low Risk: 0-6 points, Medium-Risk: 7-13 points, High-Risk: 14-17 points, and Very-High-Risk:18-22 points). Patients were considered to have a history of skin cancer if they had a registered pretransplant diagnosis of cSCC, BCC, melanoma or MCC.

We carried out a competing risk survival analysis where the event of interest was the first skin cancer occurrence after transplantation whilst death was considered the competing event. A competing event prevents the development or observation of the event of interest in a study population. Due to the higher mortality experienced by transplant recipients, accounting for competing events is usually recommended to provide accurate predictions on the probability of the event of interest.(Wolbers et al., 2014) To evaluate the power of discrimination of the tool, cumulative incidence functions were plotted to assess incidence of skin cancer by SUNTRAC group. Following the methodology used to create the SUNTRAC tool, we computed unadjusted subdistribution hazard ratios (SHR) and their 95% confidence intervals (CI) via a Fine-Gray subdistribution hazard model for every SUNTRAC group and the risk factors included in the tool.(Fine & Gray, 1999) Predictive performance was evaluated by computing Wolbers' concordance index (C-index) and by calculating time-dependent areas under the receiving operator characteristic curves (t-AUROCs) over time and truncated at 5 years after transplant.(Blanche et al., 2013, 2019; Wolbers et al., 2014) The concordance index indicates the overall discrimination ability of the model by ranking the expected survival times based on the risk attributed to each individual, a concordance index of 0.5 indicates a random prediction whilst a concordance index of 1 would indicate perfect discrimination power.(Blanche et al., 2013, 2019; Wolbers et al., 2014)

In our study we focused on assessing the discrimination power of the tool as models can always be recalibrated to provide accurate expected probabilities. Nonetheless, we assessed calibration by visual comparison of cumulative incidence functions and by comparing five-year-cumulative incidences of skin cancer in our cohort to those reported in the TSCN cohort.

We did not carry out formal sample size estimations as these methods are not well-established for validating prognostic scores. However, we included more than half the participants included in the TSCN cohort with a higher event rate than in the derivation cohort (17.6% vs. 13.6%). We also performed sensitivity analyses in which BCC was not considered as a skin cancer outcome without resulting in major changes to our estimates or overall conclusions. All tests were two-tailed, and the level of significance was set at $p<0.05$. All statistical analyses were done with R version 3.6.1 (Vienna, Austria) with the following main additional packages: *"survival", "cmprsk", "prodlim", "pec", "maxstat"* and *"rpart"*. We followed the TRIPOD reporting guidelines to describe our findings.(Moons et al., 2015)

RESULTS

Cohort characteristics

We included 3421 patients in our validation cohort (62.3% males with a median age at transplant of 53 years) of which 603 (17.6%) developed skin cancer within a median follow-up of 5.7 years after transplantation with 23213 years of contributed follow-up (Table 1). Table 1 shows detailed information on the clinical and demographic characteristics of the validation cohort stratified by country. Significant differences regarding median age at transplant, race distribution, type of transplant and posttransplant skin cancer rates were found by country, while pretransplant skin cancer history percentages were almost equal. Median SUNTRAC scores differed by country with a significantly higher median score in patients from Spain but a larger spread of scores was observed in the Dutch cohort (Table 1 & eFigure 1A). Accordingly, the distribution of patients between the SUNTRAC risk groups was quite different except for the Very-High risk group that displayed almost equal percentages (Table 1 & eFigure 1A). Age, sex and other SUNTRAC risk factors were distributed unevenly across SUNTRAC groups (eTable 1, eFigure 1B-G).

One-year and five-year skin cancer cumulative incidences were 2.12% (95% CI 1.68-2.65) and 12.14% (95% CI 10.99-13.35), respectively. Patients that developed malignancy after transplant were more commonly male, over 50 years of age, white race, had history of pretransplant skin cancer, had higher SUNTRAC total scores and belonged to higher SUNTRAC risk groups (Table 2).

All SUNTRAC variables except for type of transplant were statistically significant risk factors for developing skin cancer (Table 3). White race and previous history of skin cancer were the most relevant risk factors and most of the variables displayed very similar SHRs to those reported in the TSCN study and were used to determine the points for each variable (Table 3). On the other hand, thoracic transplant was not associated with an increased risk of skin cancer. We also tested the validity of the dichotomization of the age variable at 50 years of age and found that in our cohort the most discriminative cutpoint would be at 53 years from a survival tree model or at 52 years via a maximally selected rank statistic method.(Hothorn & Lausen, 2002) The country of origin was not an independent risk factor for developing skin cancer after adjusting for the variables in the SUNTRAC tool.

Discrimination ability

We verified that SUNTRAC scores were associated with an increased risk of skin cancer and found that, a one-point increase in the SUNTRAC score was associated with a 25% increase in the rate of skin cancer (SHR: 1.25, [95% CI: 1.22,1.28], p<0.001).

By replicating the methodology used to determine the cut-points in the total score defining the original SUNTRAC risk groups, we found that a four tier classification system also yielded the best prognostic discrimination in our cohort. The optimal cut-points in our cohort aligned almost perfectly with those from the original SUNTRAC tool with a one point offset for the first three groups and the exact same cutpoint for the Very-High-Risk group. (eTable 2)

We found statistically significant differences in the percentage of skin cancer across SUNTRAC groups with higher percentages in the higher risk groups but no differences in the distribution of the different types of skin cancer between SUNTRAC risk groups (eTable 1).

Cumulative incidence of skin cancer by SUNTRAC group are displayed in Figure 1. Higher risk groups displayed higher skin cancer incidences at all times with wide separation between curves.

By country, the SUNTRAC tool achieved greater discrimination in the case of the Dutch cohort compared to the Spanish cohort (eFigure 2).

To further assess the discrimination ability, a Fine-Gray subdistribution hazard model was fitted with the SUNTRAC group as single covariate. Significantly higher skin cancer rates were found for each increase in SUNTRAC group. In comparison to the Low-Risk group the SHR for developing skin cancer was 6.8 for the Medium-risk group ([95% CI, 3.8 - 12], p <0.001), 15.9 for the High-risk group ([95% CI, 8.9 - 28], p <0.001) and 54.8 for the Very-high-risk group ([95% CI, 29 - 103], p <0.001). Wolbers' concordance index at 5 years was 0.72 in our validation cohort whereas the reported concordance index in the TSCN cohort was 0.74 (eFigure 3). Greater power of discrimination was found at 5 years after transplant for the Dutch cohort than for the Spanish cohort (t-AUROCs: 0.75 [95%CI, 0.72,0.79] vs. 0.64 [95%CI, 0.59,0.68]). We also computed t-AUROCs of the tool at different time points eliciting quite stable performance over time (eFigure 3).

Calibration assessment

To evaluate the concordance in expected skin cancer incidences, we compared cumulative incidence curves and five-year skin cancer cumulative incidences between the validation cohort and the TSCN cohort (Figure 2A & 2B). We found quite similar predicted skin cancer incidences with slightly lower percentages in the TSCN cohort at five years after transplant (Figure 2B).

Dermatological screening times have been proposed for each SUNTRAC group.(Jambusaria-Pahlajani et al., 2019) We assessed whether those times (6 months, 1, 2 and 10 years) were adequate in the European SOTR cohort and found that our patients reached the 2% cumulative incidence threshold at fairly similar timepoints (3 months, 7 months, 2 and 6 years) (Figure 1).

Discussion

Skin cancer screening in the SOTR population is a practice recommended by several clinical practice guidelines and the American Society of Transplantation. (Acuna et al., 2017; Kasiske et al., 2000; Stasko et al., 2004) Most guidelines recommend annual screening for skin malignancies, and some recommend skin cancer risk stratification.(Acuna et al., 2017; Crow et al., 2019) The SUNTRAC tool has emerged as a risk prediction instrument that could guide this screening whilst being quick to implement and having the ability to be administered by office staff.(Jambusaria-Pahlajani et al., 2019)

This study has focused on validating the use of the SUNTRAC tool in predicting skin cancer in a large European cohort comprised of SOTR from two countries with known differences in skin cancer risk.(Ferrándiz & José Fuente, 2001) Due to the recent publication of the SUNTRAC tool our study was retrospective but based on prospectively gathered data.

Although cancer incidences varied between countries, the SUNTRAC tool was able to identify patients at a high risk of developing post-transplant skin cancer. It assigned most patients to the Medium-Risk category in the Dutch cohort, whilst most recipients in the Spanish cohort were considered High-Risk. These findings suggests that the SUNTRAC tool may prove valuable for detecting high risk patients and referring them to a dermatologist within 6 months of transplant or even assessing them before transplantation.

In comparison to the TSCN cohort there were fewer patients in the Low Risk group as white race is the main risk factor adding 9 points and the Low-Risk group goes from 0 to 6 points. This uneven distribution amongst groups will be found in other countries depending on their racial case mix. Some experts advise caution on considering transplant recipients of color as being at low risk for skin cancer as they might have a higher risk of developing Kaposi sarcoma, a skin cancer endpoint not considered in the development of the SUNTRAC tool nor in the present external validation.(Kentley et al., 2021)

Even though the Dutch cohort was solely comprised of kidney transplants, we found the best overall discrimination in this cohort. This finding could be related to differences in race and age distribution between cohorts suggesting a higher discriminative ability in countries with more racially diverse populations and with almost equal percentage of people under and over 50 years. Another explanation for these differences might be residual confounding due to the categorization of the patients into just four risk groups. This claim is supported by the fact that Dutch origin (vs. Spanish) was not a significant risk factor for skin cancer after adjusting by the SUNTRAC variables but it became a significant predictor of skin cancer after only adjusting by SUNTRAC group (data not shown).

The points assigned to the variables in the SUNTRAC tool were very similar to those that would be optimal for our cohort, suggesting that the selected variables are indeed relevant risk factors with similar relative contribution to the development of skin cancer in European populations. In our study having a thoracic transplant was not associated with an increased risk of developing skin cancer. This may be due to residual confounding as all thoracic transplant recipients came from the Spanish cohort, due to selection bias or possibly due to differences in immunosuppressive regimes in comparison to the TSCN cohort. Nonetheless, we found a fairly good prognostic discrimination just slightly below that attained in the derivation cohort.

Regarding calibration, we observed very similar skin cancer incidences to those predicted by the SUNTRAC tool. This finding seems to support the ability of the SUNTRAC tool to recommend fixed time intervals for a first dermatological screening. This tool, however, does not explicitly provide orientation on the follow-up intervals after the first dermatological screening. Such a tool would ideally integrate information on posttransplant skin cancer events, immunosuppressive or other photosensitizing medications among other time-varying clinical variables.(Carroll et al., 2003; Lowenstein et al., 2017; Urwin et al., 2009) Whilst *Urwin et al.* developed a skin cancer risk prediction tool for renal patients and offered follow-up intervals, the SUNTRAC tool provides the clinician with an intuitive skin cancer risk measure to adjust future follow-up visits based on basal skin cancer risk, regardless of the type of organ transplant and with an easy implementation.(Urwin et al., 2009) Recent attempts at incorporating genetic information to skin cancer risk prediction in SOTR have yielded marginal benefits over just using clinical information suggesting that tools based on clinical variables are still current.(Stapleton et al., 2019, 2020) Prospective randomized controlled trials would be desirable to fully assess the effect of the SUNTRAC tool in transplant centers.

Bias arising from its retrospective design, differences in study time periods and immunosuppressive regimes, incompleteness of cancer registration and from selecting only two European countries is definitely possible. In spite of these limitations, our study had several strengths such as a generous sample size and the inclusion of BCC diagnoses, a tumor that had not been previously considered in the TSCN cohort.

We conclude that the SUNTRAC tool is a useful instrument to stratify patients into skin cancer risk groups and provides fairly accurate cumulative skin cancer incidences in populations different from the TSCN study. Having a tool that can quickly and correctly stratify SOTR according to their relative skin cancer risk is a great aid for the clinician and a fundamental step in defining guidelines to ensure adequate screening and dermatological follow-up of these patients.

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Authors Contribution

AGT, CFP, SA and JBV contributed to the conception and design of the study protocol. CFP, CGC, RG, EdJ and JBV participated in the acquisition of clinical data for the validation cohorts. AGT carried out the statistical analysis under guidance and recommendations from CFP and JBV. AGT primarily wrote the manuscript with important contributions from CFP, RG, JBV and VGP. All authors approved the final version to be published, provided valuable feedback, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors critically reviewed the manuscript for intellectual content and approved the final version of the manuscript.

Disclosure

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Data availability and data analysis statement

The data that support the findings of this study are available from the corresponding author upon reasonable request. AGT and CFP had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Article Tables

Table 1: Clinical and demographic characteristics of the validation cohort by country and overall.

	Spain (n=1046)	The Netherlands (n=2375)	Validation Cohort (n=3421)	P-value†
Sex, No. (%)				0.08[a]
Female	371 (35.5%)	918 (38.7%)	1289 (37.7%)	
Male	675 (64.5%)	1457 (61.3%)	2132 (62.3%)	
Age at transplant, median (Q1-Q3), y	57.0 (48.0, 63.0)	51.0 (40.5, 61.0)	53.0 (42.0, 62.0)	< 0.001[b]
Age at transplant (over 50y), No. (%)				< 0.001[a]
No	296 (28.3%)	1117 (47.0%)	1413 (41.3%)	
Yes	750 (71.7%)	1258 (53.0%)	2008 (58.7%)	
Race, No. (%)				< 0.001[a]
Asian	7 (0.7%)	65 (2.7%)	72 (2.1%)	
Black	15 (1.4%)	122 (5.1%)	137 (4.0%)	
Latinx	51 (4.9%)	224 (9.4%)	275 (8.0%)	
Middle Eastern and North African	31 (3.0%)	78 (3.3%)	109 (3.2%)	
White	942 (90.1%)	1886 (79.4%)	2828 (82.7%)	
Type of transplant, No. (%)				< 0.001[a]
Kidney	443 (42.4%)	1976 (83.2%)	2419 (70.7%)	
Kidney-liver	9 (0.9%)	14 (0.6%)	23 (0.7%)	
Kidney-pancreas	0 (0.0%)	352 (14.8%)	352 (10.3%)	
Liver	143 (13.7%)	0 (0.0%)	143 (4.2%)	
Pancreas	0 (0.0%)	33 (1.4%)	33 (1.0%)	
Single-Lung	156 (14.9%)	0 (0.0%)	156 (4.6%)	
Double-lung	293 (28.0%)	0 (0.0%)	293 (8.6%)	
Heart-lung	1 (0.1%)	0 (0.0%)	1 (0.0%)	
Heart	1 (0.1%)	0 (0.0%)	1 (0.0%)	
Type of transplant (abdominal/thoracic), No. (%)				< 0.001[a]
Abdominal	596 (57.0%)	2375 (100.0%)	2971 (86.8%)	
Thoracic	450 (43.0%)	0 (0.0%)	450 (13.2%)	
Pretransplant history of skin cancer, No. (%)				1.00[a]
No	1008 (96.4%)	2288 (96.3%)	3296 (96.3%)	
Yes	38 (3.6%)	87 (3.7%)	125 (3.7%)	
SUNTRAC score, median (Q1-Q3), points	14.0 (11.0, 15.0)	11.0 (9.0, 15.0)	13.0 (9.0, 15.0)	< 0.001[b]
SUNTRAC group, No. (%)				< 0.001[c]
Low-Risk	93 (8.9%)	487 (20.5%)	580 (17.0%)	

	Spain (n=1046)	The Netherlands (n=2375)	Validation Cohort (n=3421)	P-value†
Medium-Risk	352 (33.7%)	1221 (51.4%)	1573 (46.0%)	
High-Risk	566 (54.1%)	587 (24.7%)	1153 (33.7%)	
Very-High-Risk	35 (3.3%)	80 (3.4%)	115 (3.4%)	
Follow-up time, median (Q1-Q3), y	3.8 (2.1, 6.7)	6.7 (3.4, 11.3)	5.7 (2.7, 9.4)	< 0.001[b]
Skin cancer after transplant, No. (%)				0.004[a]
No	891 (85.2%)	1927 (81.1%)	2818 (82.4%)	
Yes	155 (14.8%)	448 (18.9%)	603 (17.6%)	
Type of skin cancer (first event), No. (%) ††				< 0.001[a]
Basal cell carcinoma	59 (38.1%)	252 (56.2%)	311 (51.6%)	
Squamous cell carcinoma, cutaneous	90 (58.1%)	183 (40.8%)	273 (45.3%)	
Melanoma, cutaneous	6 (3.9%)	13 (2.9%)	19 (3.2%)	
Merkel cell carcinoma	0 (0%)	0 (0%)	0 (0%)	

Abbreviations: SUNTRAC, Skin and Ultraviolet Neoplasia Transplant Risk Assessment Calculator; Q1, first quartile; Q3, third quartile;y, years

† P-values from tests comparing Spain vs. The Netherlands. †† **Percentages calculated for those who developed a skin cancer event.**

[a] Fisher's exact test for count data, [b]Kruskal-Wallis rank sum test, [c] Trend test for ordinal variables

Table 2: Clinical and demographic characteristics by skin cancer outcome after transplant and by country.

	Spain (n=1046)			The Netherlands (n=2375)			Validation Cohort (n=3421)		
	No skin cancer (n=891)	Skin cancer (n=155)	P-value	No skin cancer (n=1927)	Skin cancer (n=786)	P-value	No skin cancer (n=2818)	Skin cancer (n=603)	P-value
Sex, No. (%)			0.006[a]			< 0.001[a]			< 0.001[a]
Female	331 (37.1%)	40 (25.8%)		780 (40.5%)	138 (30.8%)		1111 (39.4%)	178 (29.5%)	
Male	560 (62.9%)	115 (74.2%)		1147 (59.5%)	310 (69.2%)		1707 (60.6%)	425 (70.5%)	
Age at transplant, median (Q1-Q3), y	56.0 (46.0, 63.0)	60.0 (55.0, 67.0)	< 0.001[b]	49.0 (39.0, 59.5)	58.0 (48.0, 66.0)	< 0.001[b]	51.0 (41.0, 61.0)	58.0 (50.0, 66.0)	< 0.001[b]
Age at transplant (over 50y), No. (%)			< 0.001[a]			< 0.001[a]			< 0.001[a]
No	278 (31.2%)	18 (11.6%)		996 (51.7%)	121 (27.0%)		1274 (45.2%)	139 (23.1%)	
Yes	613 (68.8%)	137 (88.4%)		931 (48.3%)	327 (73.0%)		1544 (54.8%)	464 (76.9%)	
Race, No. (%)			< 0.001[a]			< 0.001[a]			< 0.001[a]
Asian	7 (0.8%)	0 (0.0%)		62 (3.2%)	3 (0.7%)		69 (2.4%)	3 (0.5%)	
Black	15 (1.7%)	0 (0.0%)		119 (6.2%)	3 (0.7%)		134 (4.8%)	3 (0.5%)	
Latinx	50 (5.6%)	1 (0.6%)		219 (11.4%)	5 (1.1%)		269 (9.5%)	6 (1.0%)	
Middle Eastern and North African	31 (3.5%)	0 (0.0%)		76 (3.9%)	2 (0.4%)		107 (3.8%)	2 (0.3%)	
White	788 (88.4%)	154 (99.4%)		1451 (75.3%)	435 (97.1%)		2239 (79.5%)	589 (97.7%)	
Type of transplant, No. (%)			0.004[a]			-			< 0.001[a]
Abdominal	491 (55.1%)	105 (67.7%)		1927 (100.0%)	448 (100.0%)		2418 (85.8%)	553 (91.7%)	
Thoracic	400 (44.9%)	50 (32.3%)		0 (0%)	0 (0%)		400 (14.2%)	50 (8.3%)	
Pretransplant history of skin cancer, No. (%)			0.002[a]			< 0.001[a]			< 0.001[a]
No	866 (97.2%)	142 (91.6%)		1898 (98.5%)	390 (87.1%)		2764 (98.1%)	532 (88.2%)	
Yes	25 (2.8%)	13 (8.4%)		29 (1.5%)	58 (12.9%)		54 (1.9%)	71 (11.8%)	
SUNTRAC score, median (Q1-Q3), points	14.0 (11.0, 15.0)	15.0 (14.0, 15.0)	< 0.001[b]	11.0 (9.0, 13.0)	15.0 (11.0, 15.0)	< 0.001[b]	11.0 (9.0, 15.0)	15.0 (13.0, 15.0)	< 0.001[b]

	Spain (n=1046)			The Netherlands (n=2375)			Validation Cohort (n=3421)		
	No skin cancer (n=891)	**Skin cancer (n=155)**	**P-value**	**No skin cancer (n=1927)**	**Skin cancer (n=786)**	**P-value**	**No skin cancer (n=2818)**	**Skin cancer (n=603)**	**P-value**
SUNTRAC group, No. (%)			< 0.001[c]			< 0.001[c]			< 0.001[c]
Low-Risk	92 (10.3%)	1 (0.6%)		476 (24.7%)	11 (2.5%)		568 (20.2%)	12 (2.0%)	
Medium-Risk	321 (36.0%)	31 (20.0%)		1026 (53.2%)	195 (43.5%)		1347 (47.8%)	226 (37.5%)	
High-Risk	456 (51.2%)	110 (71.0%)		398 (20.7%)	189 (42.2%)		854 (30.3%)	299 (49.6%)	
Very-High-Risk	22 (2.5%)	13 (8.4%)		27 (1.4%)	53 (11.8%)		49 (1.7%)	66 (10.9%)	

Abbreviations: SUNTRAC, Skin and Ultraviolet Neoplasia Transplant Risk Assessment Calculator; Q1, first quartile; Q3, third quartile;y, years

[a] Fisher's exact test for count data, [b]Kruskal-Wallis rank sum test, [c] Trend test for ordinal variables

Table 3: Subdistribution Hazard Ratios (SHR) and their 95% confidence intervals (CI) from a multivariate competing risk regression by country and overall and those reported in the TSCN cohort for the SUNTRAC items. Corresponding points for risk factors included the Skin and Ultraviolet Neoplasia Risk Assessment Calculator (SUNTRAC).

	SHR (95% CI)				SUNTRAC points
SUNTRAC item	**Spain (n=1046)**	**The Netherlands (n=2375)**	**Validation Cohort (n=3421)**	**TSCN cohort (n=6340)**	
Race (white)	11.48 (1.63, 80.94)	8.07 (4.66,14.00)	8.38 (4.95, 14.21)	8.78 (6.05,12.76)	9
Pretransplant skin cancer (yes)	2.66 (1.46, 4.85)	4.67 (3.29, 6.64)	4.02 (3, 5.38)	4.59 (3.45,6.1)	6
Age at transplant (≥ 50y)	2.59 (1.58, 4.25)	2.63 (2.13, 3.24)	2.68 (2.21, 3.23)	2.46 (2.03,2.98)	4
Sex (male)	1.46 (1.02, 2.09)	1.49 (1.21, 1.83)	1.47 (1.23, 1.75)	1.53 (1.29,1.82)	2
Type of transplant (thoracic)	0.62 (0.44, 0.87)	-	0.6 (0.45, 0.82)	1.28 (1.08,1.53)	1