Validity of the Skin and UV Neoplasia Transplant Risk Assessment Calculator (SUNTRAC) tool in a Dutch cohort of transplant recipients

TransplantLines Investigators; Bacos-Cosma, Octavian; Sidorenkov, Grigory A.; Kremer, Daan; Knobbe, Tim J.; van der Vegt, Bert; Bakker, Stephan J. L.; Racz, Emoke

Published in:
JEADV Clinical Practice

DOI:
10.1002/jvc2.555

Received: 11 June 2024 | Revised: 19 August 2024 | Accepted: 25 September 2024

DOI: 10.1002/jvc2.555

JEADV CLINICAL PRACTICE
OPEN ACCESS JOURNAL OF THE EUROPEAN ACADEMY OF DERMATOLOGY & VENEREOLOGY

ORIGINAL ARTICLE

Validity of the Skin and UV Neoplasia Transplant Risk Assessment Calculator (SUNTRAC) tool in a Dutch cohort of transplant recipients

Octavian I. Bacoș-Cosma[1] | Grigory A. Sidorenkov[2] | Daan Kremer[3] | Tim J. Knobbe[3] | Bert van der Vegt[4] | Stephan J. L. Bakker[3] | Emőke Rácz[1] | TransplantLines Investigators

[1]Department of Dermatology, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands

[2]Department of Epidemiology & Radiology, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands

[3]Department of Nephrology, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands

[4]Department of Pathology, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands

Correspondence
Emőke Rácz, Department of Dermatology, University Medical Center Groningen, University of Groningen, Hanzeplein 1, 9700RB, P.O. Box 30001, Groningen, the Netherlands.
Email: e.racz@umcg.nl

Funding information
The TransplantLines Biobank and Cohort study was supported by a grant from Astellas BV and Chiesi Pharmaceuticals BV, and co- financed by the Dutch Ministry of Economic Affairs and Climate Policy by means of the PPP-allowance made available by the Top Sector Life Sciences & Health to stimulate public-private partnerships. The funders had no role in the study design, data collection, analysis, reporting, or the decision to submit for publication.

Abstract

Background: To identify patients with high risk of skin cancer, risk prediction tools have been developed.

Objectives: External validation of the Skin and UV Neoplasia Transplant Risk Assessment Calculator (SUNTRAC) in a Dutch cohort of solid organ transplant recipients (SOTR) and exploration of the possibility of incorporating additional risk factors to enhance its predictive performance.

Methods: We used data from the ongoing, prospective TransplantLines Biobank and Cohort Study of the University Medical Center Groningen (Groningen, The Netherlands). We conducted a survival analysis using Fine and Gray models to determine the subdistribution hazard ratios of the SUNTRAC risk factors and groups, Wolbers C index to assess its discriminative power, and cumulative incidences of skin cancer to assess its calibration. We applied the same methods for the incorporation of additional risk factors to the model.

Results: A total of 2099 patients were included with a median age at transplantation of 52.1 years (Interquartile range [IQR]: 40.6–60.1) and a median follow-up time of 6.6 years (IQR: 3.4–12.5). In total 478 (22.8%) patients developed skin cancer. Basal cell carcinoma (53.3%) and cutaneous squamous cell carcinoma (42.9%) were most prevalent. The cumulative incidences of skin cancer per SUNTRAC risk group at 10 years were: low-risk (1.8%), medium-risk (12.9%), high-risk (34.3%) and very high-risk (68.6%). Significantly different skin cancer risk rates were observed for the medium-risk (SHR = 9.9, 95% CI: 2.51–39.4), high-risk (SHR = 21.5, 95% CI: 5.40–85.2) and very high-risk (SHR = 80.3, 95% CI: 19.26–335.1) groups in reference to the low-risk group. Wolbers C-index at

5 years was 0.71. The model was well calibrated for our cohort. The addition of other potential risk factors yielded no or marginal improvement of discriminative value on top of SUNTRAC.

Conclusions: SUNTRAC is valid for the general Dutch SOTR population, and it can be clinically implemented.

KEYWORDS

solid organ transplant recipients, skin cancer, SUNTRAC, screening

INTRODUCTION

Skin cancer is the most common malignancy after solid organ transplantation[1] with an estimated incidence of 1437 per 100,000 person-years.[2] Skin cancer-related mortality is nine times higher in solid organ transplant recipients (SOTR)[3] compared to the general population, therefore screening SOTR for skin cancer is important for decreasing the disease burden in this population.[4] However, healthcare resources are limited, rendering screening all organ transplant recipients unfeasible. Prioritising screening for patients with the highest risk for skin cancer is essential.[4] Risk prediction tools that incorporate combinations of known risk factors have been developed to identify and stratify patients at risk.[5,6] However, most of these tools have been tested only in cohorts of white kidney transplant recipients, raising concerns about their validity for the general SOTR population. Additionally, some of these tools include risk factors that are difficult to quantify, such as sun exposure. For these reasons, these tools have not been widely adopted.[7]

Jambusaria-Pahlajani et al.[8] developed the Skin and Ultraviolet Neoplasia Transplant Risk Assessment Calculator (SUNTRAC) that employs five easily determinable risk factors, including sex, age at transplantation, pre-transplant history of skin cancer, race, and type of transplantation (Table 1). According to their overall score patients are assigned to one of four risk categories. SUNTRAC proposes to start regular dermatological screening when the cumulative incidence of skin cancer per risk group reaches the 2% threshold (as determined by a US-based Delphi expert panel[4]). This would correspond to starting dermatological screening 6 months, 1 year, 2 years and 10 years after transplantation for the very high-risk, high-risk, medium-risk and low-risk groups, respectively. To ensure that the SUNTRAC tool is user-friendly, its creators have made it available as a smartphone application.

In 2022, Gómez-Tomás et al.[9] validated the SUNTRAC tool in a large cohort including 3421 patients from two European countries, Spain and the Netherlands. Their study found that the SUNTRAC tool is generalisable to their cohort of patients. The Dutch cohort in this study consisted exclusively of kidney transplant recipients.

TABLE 1 Points given per risk factor present and their distribution per risk group per the instructions of Jambusaria-Pahlajani et al.[8]

SUNTRAC risk factor[a]	Points[b]	Risk groups[c]
White race	9	Low risk (0–6)
Pre-transplant history of skin cancer	6	Medium risk (7–13)
Age ≥ 50 years at transplantation	4	High risk (14–17)
Male sex	2	Very high risk (18–22)
Thoracic transplant	1	

Abbreviation: SUNTRAC, Skin and UV Neoplasia Transplant Risk Assessment Calculator.

[a]Risk factors included in the SUNTRAC.

[b]Points given per risk factor present.

[c]Distribution of points per risk group according to SUNTRAC.

The objectives of our study were to externally validate the SUNTRAC tool in a Dutch cohort that includes transplant recipients of diverse organs, to strengthen the generalisability of the tool for the Dutch population. Furthermore, we assessed the value of adding two other potential risk factors for skin cancer to the SUNTRAC model, that can be objectively determined and easily quantified around transplantation: Body mass index (BMI) and the total number of Human Leucocyte Antigen (HLA) mismatches. These have been previously identified as relevant risk factors for skin cancer in SOTR.[10–13] SUNTRAC estimates the risk of developing skin cancer at the time of transplantation, therefore post-transplant risk factors such as various types of immunosuppressive regimens were not included in the analysis.

METHODS

TransplantLines cohort and biobank study

We used data from the TransplantLines Biobank and Cohort[14] (ClinicalTrials.gov identifier: NCT03272841), a large cohort including SOTR and living organ donors (≥18 years) of the University Medical Center Groningen (Groningen, The Netherlands). All participants gave written informed consent. The study was initiated in 2015 and currently includes more than 2000 SOTR. Inclusion is ongoing. The study protocol was approved by the local Institutional Review Board (METc 2014/077) and adheres to the UMCG Biobank Regulation and the Declarations of Helsinki and Istanbul.

Study population

We included a total of 2099 adult solid organ transplant recipients (i.e., kidney, liver, lung, heart, pancreas, and small intestine), who were transplanted between 1977 and February 2021 (1 year before end of follow-up, to allow enough time for skin cancer to occur) with 80% of the transplants from 2005 onwards. The end follow-up date was 2 February 2022.

Study outcomes

The primary outcome was time between first transplantation and first skin cancer diagnosis. The event of interest, skin cancer, was censored for death. The captured skin cancer diagnoses included cutaneous squamous cell carcinoma (cSCC), basal cell carcinoma (BCC), melanoma (MM) and Merkel cell carcinoma (MCC). Although BCC does not impact mortality rates as opposed to other skin cancer types, we chose to include it because of its debilitating outcomes if left untreated. Data on skin cancer diagnoses was obtained from the Pathologisch-Anatomisch Landelijk Geautomatiseerd Archief (Palga), a nationwide network for registration, storage, and sharing of pathological data. Palga records all pathologically diagnosed cancers for each patient. Skin cancers that occurred earlier than 6 months after transplantation were considered pre-existent.

Exposure variables

The influences of sex (male or female), age at transplantation (<50 or ≥50 years), pre-transplant skin cancer (yes or no; including only: cSCC, BCC, MM, MCC), race (White or Non-white: Asian, Black, Other) and type of transplantation (abdominal or thoracic) on skin cancer risk in SOTR were evaluated. Individuals who underwent dual organ transplantation, with one of the organs being thoracic, were categorised as recipients of thoracic transplants.

In addition, the effects of the total number of HLA mismatches (HLA-A, HLA-B, HLA-DR) and BMI on skin cancer risk were analysed both as continuous and dichotomous variables. To explore the effects of HLA mismatches on skin cancer, we took each point on the scale from 0 to 6 and divided the data into groups. For each point on the scale (0–6), we created two groups: one with patients having HLA mismatches below or equal to that point, and the other with patients having HLA mismatches above that point. BMI was dichotomised at specific transition points: at overweight (BMI ≥ 25 kg/m^2), from overweight to obese (BMI ≥ 30 kg/m^2), and subsequently at each integer point from 31 to and including 35 kg/m^2.

Statistical analysis

External validation of the SUNTRAC tool

Baseline characteristics were summarised as counts and percentages or by presenting the median value with the interquartile range (IQR).

Survival analysis was conducted using a multivariate Fine and Gray subdistribution hazard (FGR) model,[15] accounting for death as a competing risk.

SUNTRAC score was calculated at the time of transplantation for each patient per the instructions of the original study (Table 1). According to their overall score, patients were assigned to a risk group: low-risk (0–6), medium-risk (7–13), high-risk (14–17) or very high-risk (18–22).

A new FGR model was fitted with the SUNTRAC risk group as the only covariate. SHRs per risk group reflect the effect size in reference to the low-risk group. Cumulative incidences of skin cancer per risk group were plotted and interpreted from a visual and numerical standpoint. We then assessed how well the model can discriminate between different risk groups by computing Wolbers C-index and the time-dependent area under the receiving operating curve (t-AUROC) at different timepoints.[16,17]

To identify the maximum discriminative power possible in our cohort, we refined the model by deriving optimal cut points for the risk groups in our cohort using decision trees and recursive partitioning.[18] Patients were then assigned to these adjusted risk groups, and we

evaluated the model's performance using the same methods as for the original model. We assessed calibration by comparing the cumulative incidences of skin cancer in our cohort to the ones obtained by previous studies. Additionally, we compared the obtained dermatological screening times per risk group, defined as the moment when the 2% incidence threshold for skin cancer within each risk group was reached, to the dermatological screening times proposed by Jambusaria-Pahlajani et al.

Exploration of the additional risk factors

Each of the additional exposure variables was fitted together with the original SUNTRAC risk factors into a FGR model. To account for missing values, we used multivariate imputation by chained equations (MICE).[19] We determined the SHRs and the value thresholds for significance of the additional risk factors. After determining the SHRs, we calculated point scores by dividing the beta-coefficients of the SHRs by the smallest coefficient and rounding them to the nearest integer point, following the methods used by Jambusaria-Pahlajani et al. We then created new risk groups and tested the discriminative power of the new prediction model using the same methods as for the external validation process.

All statistical analysis of the data was performed in R statistical software, version 4.3.1 and we used the following packages: 'cmprsk', 'prodlim', 'pec', 'rpart', 'timeROC', 'mice' and 'riskRegression'. We applied a two-sided 5% level of significance.

RESULTS

Baseline characteristics

From the total of 2099 patients in our study, 1235 (58.8%) were male. The median age at transplantation was 52.1 years (IQR: 40.6–61.1) and the median follow-up was 6.6 (IQR: 3.4–12.5) years. Most patients were white (94%) and abdominal transplantations were the most common (81.6%). In total there were 1254 (59.7%) kidney transplant recipients, 417 (19.9%) liver transplant recipients, 282 (13.5%) lung transplant recipients, 97 (4.6%) heart transplant recipients and 49 (2.3%) recipients of combined transplantations. There were 101 patients (4.8%) with pre-transplant history of skin cancer. The median BMI was 24.9 kg/m^2 (IQR: 22.4–28.0 kg/m^2) and 13.9% of the patients were in the obese range. The median total HLA mismatches was 4 (IQR: 2–5).

Skin cancer occurred in 476 (22.8%) of the patients. Of the other patients, 178 (8.5%) died before developing skin cancer, and 1443 (68.7%) of the patients did not experience an event by the end of the study. The most common types of skin cancer (recorded as first events after transplantation) were BCC (53.3%) and cSCC (42.9%), while melanoma occurred in only 3.8% and MCC occurrence was not recorded. The median SUNTRAC score was 13 (IQR: 11–15) and most patients were assigned to the medium (55.8%) and high-risk (34%) groups. An overview of the demographic and clinical characteristics of the cohort is presented in Table 2.

External validation of the SUNTRAC tool

Subdistribution hazard ratios of the SUNTRAC risk factors

The SHRs for age ≥50 years (SHR = 2.27, 95% CI: 1.88–2.73), male sex (SHR = 1.23, 95% CI: 1.01–1.49) and pre-transplant history of skin cancer (SHR = 4.13, 95% CI: 2.82–6.03) were comparable to the ones obtained by the previous two studies (Table 3). In our cohort, white race had a higher subdistribution hazard ratio (SHR = 11.50, 95% CI: 2.89–45.79). Thoracic transplant was not a significant risk factor for skin cancer in our cohort.

Cumulative incidences of skin cancer

The cumulative incidences of skin cancer at 1, 5, and 10 years were 1.1%, 9.9%, and 20.8% respectively. Cumulative incidences of skin cancer per risk group at 10 years were 1.8%, 12.9%, 34.3%, and 68.6% for the low-risk, medium-risk, high-risk, and very high-risk groups respectively. There was a clear difference in skin cancer rates between groups and the cumulative incidence plots did not intersect at any time as displayed in Figure 1.

Discriminative performance

Every 1-point increase in the SUNTRAC score corresponded to a SHR of 1.23 (95% CI: 1.19–1.27, $p < 0.001$) for skin cancer. Patients at medium-risk (SHR = 9.9, 95% CI: 2.51–39.4, $p < 0.001$), high-risk (SHR = 21.5, 95% CI: 5.40–85.2, $p < 0.001$) and very high-risk group (SHR = 80.3, 95% CI: 19.26–335.1, $p < 0.001$) had considerably higher skin cancer rates than those in the low-risk group. Wolbers C-index was 0.71 at 5 years, and the t-AUROC was 0.73 (95% CI: 0.68–0.77) indicating moderate to good performance. The performance of the model remained stable over time with a gradual decline after the 10-year mark.

Like in the derivation[8] cohort, the ideal score distribution that achieved the best discriminative power in our cohort was a 4-tier system, albeit with a wider interval for

TABLE 2 Clinical and demographic characteristics of the cohort per outcome and in general.

Characteristic	Patients, No (%)			
	No skin cancer No = 1443	Skin cancer No = 478	Death No = 178	Total No = 2099
Sex				
Men	841 (58.3)	293 (61.3)	101 (56.7)	1235 (58.8)
Women	602 (41.7)	185 (38.7)	77 (43.3)	864 (41.2)
Age at Transplantation				
Median (Q1–Q3)	50.8 (38.4–59.8)	54.1 (44.6–62.5)	57.8 (47.1–66.4)	52.1 (40.6–61.1)
<50 years	696 (48.2)	182 (38.1)	58 (32.6)	936 (44.6)
≥50 years	747 (51.8)	296 (61.9)	120 (67.4)	1163 (55.4)
Race				
White	1327 (92.0)	476 (99.6)	170 (95.5)	1973 (94.0)
Black	29 (2.0)	0 (0.0)	1 (0.6)	30 (1.4)
Asian	46 (3.2)	2 (0.4)	3 (1.7)	51 (2.4)
Other	41 (2.8)	0 (0.0)	4 (2.2)	45 (2.2)
Type of first transplant				
Kidney	877 (60.8)	274 (57.3)	99 (55.6)	1250 (59.6)
Kidney and Pancreas	21 (1.5)	6 (1.3)	1 (0.6)	28 (1.3)
Kidney and Liver	6 (0.4)	1 (0.2)	1 (0.6)	8 (0.4)
Double-kidney	0 (0.0)	2 (0.4)	2 (1.1)	4 (0.2)
Liver	286 (19.8)	101 (21.1)	30 (16.9)	417 (19.9)
Liver and lungs	3 (0.2)	0 (0.0)	0 (0.0)	3 (0.1)
Liver and Pancreas	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.0)
Liver, Intestine and Pancreas	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.0)
Single-lung	12 (0.8)	10 (2.1)	11 (6.2)	33 (1.6)
Double-lung	167 (11.6)	55 (11.5)	27 (15.2)	249 (11.9)
Heart	65 (4.5)	26 (5.4)	6 (3.4)	97 (4.6)
Heart and Lungs	2 (0.1)	3 (0.6)	1 (0.6)	6 (0.3)
Intestine	2 (0.1)	0 (0.0)	0 (0.0)	2 (0.1)
Abdominal or thoracic transplant				
Abdominal	1194 (82.7)	384 (80.3)	133 (74.7)	1711 (81.5)
Thoracic	249 (17.3)	94 (19.7)	45 (25.3)	388 (18.5)
History of skin cancer				
No	1406 (97.4)	424 (88,7)	168 (94.4)	1998 (95.2)
Yes	37 (2.6)	54 (11.3)	10 (5.6)	101 (4.8)
SUNTRAC score, points				
Median (Q1–Q3)	12.0 (10.0–15.0)	13.0 (11.0–15.0)	13.0 (11.0–15.0)	13.0 (11.0–15.0)
SUNTRAC risk groups				
Low	114 (7.9)	2 (0.4)	7 (3.9)	123 (5.9)
Medium	844 (58.5)	240 (50.2)	87 (48.9)	1171 (55.8)
High	453 (31.4)	187 (39.1)	74 (41.6)	714 (34.0)
Very high	32 (2.2)	49 (10.3)	10 (5.6)	91 (4.3)

(Continues)

TABLE 2 (Continued)

Characteristic	Patients, No (%)			
	No skin cancer No = 1443	Skin cancer No = 478	Death No = 178	Total No = 2099
Median follow-up time (Q1–Q3) in years	6.5 (3.5–12.5)	6.8 (3.0–12.6)	7.0 (3.3–12.4)	6.6 (3.4–12.5)
BMI				
Median (Q1–Q3) kg/m^2	25 (22.4–28.1)	24.6 (22.3–27.1)	25.6 (23–28)	24.9 (22.4–28)
≥25 kg/m^2	708 (49.1)	201 (42.1)	100 (56.2)	1009 (48.1)
≥30 kg/m^2	222 (15.4)	42 (8.8)	27 (15.2)	291 (13.9)
≥32 kg/m^2	121 (8.4)	15 (3.1)	17 (9.6)	153 (7.3)
≥35 kg/m^2	38 (2.6)	2 (0.4)	7 (3.9)	47 (2.2)
Missing values	11 (0.8)	14 (2.9)	2 (1.1)	27 (1.3)
Total HLA mismatches				
Median (Q1–Q3) mismatches	4 (2–5) mismatches	4 (2–5) mismatches	4 (3–5) mismatches	4 (2–5) mismatches
0	76 (5.3)	29 (6.1)	13 (7.3)	118 (5.6)
1	54 (3.7)	19 (4.0)	7 (3.9)	80 (3.8)
2	185 (12.8)	58 (12.1)	14 (7.9)	257 (12.2)
3	288 (20.0)	87 (18.2)	31 (17.4)	406 (19.3)
4	242 (16.8)	75 (15.7)	32 (18.0)	349 (16.6)
5	242 (16.8)	70 (14.6)	27 (15.2)	339 (16.2)
6	158 (10.9)	60 (12.6)	31 (17.4)	249 (11.9)
Missing values	198 (13.7)	80 (16.7)	25 (12.9)	301 (14.3)

Abbreviations: BMI, Body mass index; HLA, Human leucocyte antigen; Q, quartile; SUNTRAC, Skin and UV Neoplasia Transplant Risk Assessment Calculator.

TABLE 3 Subdistribution hazard ratios (SHR) of the SUNTRAC risk factors across studies.

SUNTRAC risk factor	SHR (95% CI)		
	Our cohort	First validation cohort	Derivation cohort
White race	11.50 (2.89–45.72)	8.38 (4.95–14.21)	8.78 (6.05–12.76)
Pre-transplant history of skin cancer	4.13 (2.82–6.03)	4.02 (3–5.38)	4.59 (3.45–6.1)
Age ≥ 50 years at transplantation	2.27 (1.88–2.73)	2.68 (2.2–3.23)	2.46 (2.03–2.98)
Male sex	1.23 (1.01–1.49)	1.47 (1.23–1.75)	1.53 (1.29–1.82)
Thoracic transplant	1.10 (0.87–1.39)	0.60 (0.45–0.82)	1.28 (1.08–1.53)

Abbreviations: CI, confidence interval; SHR, Subdistribution hazard ratio; SUNTRAC, Skin and UV Neoplasia Transplant Risk Assessment Calculator.
Note: SHR of the risk factors included in the SUNTRAC and their 95% CI when fitted in a multivariate Fine and Gray model.

the low-risk group (0–7 points) and high-risk group (13–17 points) and a narrower interval for the medium-risk group (8–12 points). The cut-off for the very high-risk group was the same (18 points). The discrimination achieved by this system was only marginally superior (Wolbers C-index = 0.74, t-AUROC = 0.76 (95% CI: 0.73–0.79), t = 5 years) to the original 4-tier system.

Calibration

We found that the model was well calibrated for our cohort with similar cumulative incidences across risk groups compared to the derivation cohort (Figure 2). In our cohort, the 2% skin cancer incidence threshold was reached after 7 months in the very high-risk group, after 1 year and 4 months in the high-risk group and after

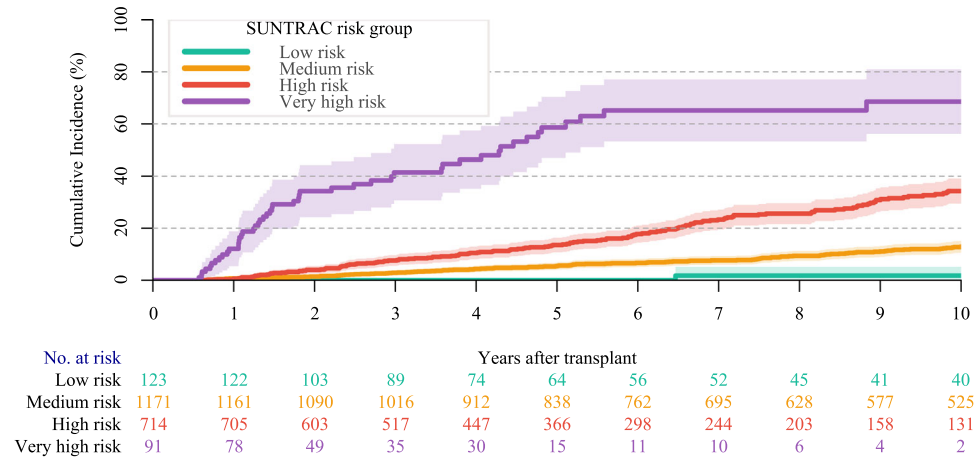

FIGURE 1 Cumulative incidence of skin cancer after solid organ transplantation per SUNTRAC risk group.

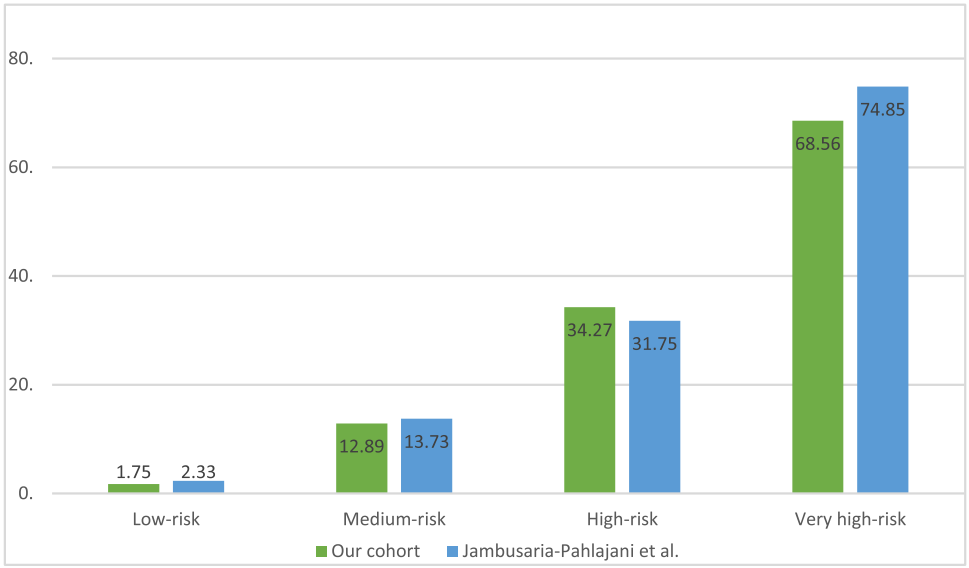

FIGURE 2 Cumulative incidence of skin cancer per SUNTRAC risk group at 10 years compared with the derivation cohort.

2 years and 4 months in the medium-risk group. In the low-risk group, the 2% incidence threshold was not reached within 10 years.

Exploration of additional risk factors

HLA mismatch and BMI were fitted together with the other SUNTRAC variables in a FGR model. We observed a slight increase in skin cancer rates for every unit increase in the total number of HLA mismatches (SHR = 1.02, 95% CI: 0.97–1.08), however, this finding was not statistically significant. Further analysis at each unit for HLA mismatching did not yield statistically significant results. Regarding BMI, every 1-unit increase was associated with a decrease in the risk of skin cancer [SHR = 0.976 (95% CI: 0.95–0.99, $p < 0.05$)]. After BMI categorisation, the threshold for statistical significance was found to be a BMI equal to or higher than 32 kg/m^2 [SHR (95% CI): 0.53 (0.31–0.90)]. The effect size of the SUNTRAC risk factors remained stable when adjusted for the new variables (Table 4).

Discriminative ability of the adjusted model

The wide SHR confidence interval for race (Table 4) prevented us from determining an accurate point score for this risk factor in our cohort, therefore it was omitted from further analysis. We also omitted the type of transplantation and the total number of HLA mismatches as these risk factors were not significantly associated with skin cancer in our cohort. We fitted a new FGR model with only the dichotomous BMI at the

TABLE 4 Subdistribution hazard ratios (SHR) of all the risk factors fitted together in a multivariate Fine and Gray model, *p-value < 0.05

Risk factor	SHR (95% CI)
White race	11.81 (2.97–46.94)*
Pre-transplant history of skin cancer	4.14 (2.84–6.06)*
Age ≥ 50 years at transplantation	2.28 (1.90–2.76)*
Male sex	1.21 (1.00–1.47)*
Thoracic transplant	1.04 (0.81–1.32)
BMI ≥ 32	0.53 (0.31–0.90)*
Total number of HLA mismatches	1.02 (0.96–1.08)

Abbreviations: BMI, Body mass index; HLA, Human Leucocyte Antigen; SHR, Subdistribution hazard ratio.

point value of 32 kg/m^2, sex, age, and pre-transplant history of skin cancer. The point scores derived from their SHRs were: eight points for pre-transplant history of skin cancer, five points for age older than 50 years, three points for BMI below 32 kg/m^2 and one point for male sex. Through recursive partitioning, we derived a 3-tier risk group system: moderate-risk (0–5), high-risk (6–12), very high-risk (13–17). The Wolbers C index at 5 years for this model was 0.73.

DISCUSSION

This study provides external validation of the SUNTRAC tool in a large cohort of SOTR. Notably, our cohort stands out for its diversity of transplanted organs. Indeed, SUNTRAC risk factors showed similar effect sizes in our cohort when compared to the previous studies. We found that SUNTRAC was well calibrated to our cohort, with similar cumulative incidences of skin cancer compared to the previous studies.

The reported similar effect sizes of the risk factors used by SUNTRAC across studies suggest that they are generalisable to different populations. In our cohort, white race had a higher effect size but also wider confidence intervals which can be explained by the lower number of nonwhite patients with skin cancer compared to the other cohorts. Interestingly, thoracic transplant was not a statistically significant risk factor for skin cancer, this finding was also reported by Gómez-Tomás et al. This might be due to differences in immunosuppressive regimens between the European cohorts and the US-based derivation cohort.[9] Another possible explanation can be the inclusion of BCCs as a possible outcome in our study. Moreover, thoracic transplant is the least influential factor in the SUNTRAC model, since it only accounts for one point, and its effect may be more visible in larger cohorts such as the SUNTRAC derivation study.

Despite our cohort being less racially diverse, we observed similar cumulative incidences of skin cancer per risk group over time. This suggests that SUNTRAC has the capacity to accurately predict the risk of developing skin cancer in other cohorts irrespective of the distribution of patients within risk groups.

Our second objective was to explore other risk factors for skin cancer and assess their effect on the model. We found that when adjusted for other risk factors, a BMI higher than 32 kg/m^2 is significantly associated with a lower risk for skin cancer. The relation between BMI and skin cancer in SOTR has been previously reported, one study found that liver transplant recipients with a BMI ≤ 40 kg/m^2 have an increased risk of developing non-melanoma skin cancer.[10] However, this relation appears to be a correlation rather than a causation. One hypothesis proposes that BMI might function as a surrogate indicator for decreased sun exposure, a significant risk factor for non-melanoma skin cancer.[11]

The total number of HLA mismatches was not a significant risk factor for skin cancer in our cohort. One large cohort study found that a higher number of HLA mismatches offers a statistically significant protective effect against cSCC, MM and MCC.[12] However, in the subsequent subgroup analysis, this protective effect was statistically significant only in heart and lung transplant recipients and not in liver, kidney, and pancreas recipients. Another study found that renal transplant recipients who were heterozygous and homozygous mismatched for HLA-B antigens have an increased risk for cSCC compared to patients with no mismatches.[13] Subgroup analysis was not possible in our cohort due to limited available data.

Incorporating BMI into SUNTRAC led only to a slight increase in the discriminative power of the model which is too small to justify changing the tool. Especially when considering that BMI would be the most difficult risk factor to determine which increases the time required to compute the SUNTRAC score. Despite this, we showed that a modified SUNTRAC model achieves relatively good discriminative power in our population even when the most influential factor (race) is taken out of the model.

Although the additional risk factors did not significantly enhance the performance of the SUNTRAC tool, there are other risk factors worth exploring such as the Fitzpatrick skin phototype[20] or the presence of actinic keratosis at the time of transplantation.[21] Through incorporating additional risk factors, the overall risk of a patient can be more accurately determined which leads to safe screening postponement and a more efficient screening system. Currently, over 90% of the patients in

our cohort would get the recommendation of screening within 2 years after transplantation.

Strengths and limitations

Our study strengthened the generalisability of the SUNTRAC tool for the Dutch population by exploring its performance in a large cohort of transplant recipients of various organs. Another strength of our research is the utilisation of the Palga registry for monitoring skin cancer diagnoses, ensuring comprehensive outcome registration due to its nationwide coverage.

Limitations of this research include the inability to accurately determine SHRs for race, as well as incomplete data on HLA mismatching and BMI. Additionally, the study's single-center design and retrospective approach introduce the risk for bias.

CONCLUSION

We conclude that SUNTRAC is a valid screening tool for the Dutch population and can be clinically implemented for all types of solid organ transplantations. Future studies should focus on exploring additional risk factors that can improve the performance of the SUNTRAC tool while maintaining its ease of use.

AUTHOR CONTRIBUTIONS

Substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data: Octavian I. Bacoș-Cosma, Grigory A. Sidorenkov, Daan Kremer, Tim J. Knobbe, Bert van der Vegt, TransplantLines Investigators, Stephan J.L. Bakker, Emőke Rácz. Drafting the article or revising it critically for important intellectual content: Octavian I. Bacoș-Cosma, Grigory A. Sidorenkov, Daan Kremer, Tim J. Knobbe, Bert van der Vegt, Stephan J.L. Bakker, Emőke Rácz. Final approval of the version to be published: Octavian I. Bacoș-Cosma, Grigory A. Sidorenkov, Daan Kremer, Tim J. Knobbe, Bert van der Vegt, Stephan J.L. Bakker, Emőke Rácz.

ACKNOWLEDGEMENTS

We want to thank all patients for their contribution to this research. The TransplantLines Biobank and Cohort study was supported by a grant from Astellas BV and Chiesi Pharmaceuticals BV, and co-financed by the Dutch Ministry of Economic Affairs and Climate Policy by means of the PPP-allowance made available by the Top Sector Life Sciences & Health to stimulate public-private partnerships. The funders had no role in the study design, data collection, analysis, reporting, or the decision to submit for publication.

CONFLICTS OF INTEREST STATEMENT

The UMCG has received grants from the following companies: OWKIN, GE Healthcare, and Visiopharm. BvdV has served as a consultant or speaker for Philips, MSD/Merck, Daiichi-Sankyo/AstraZeneca, DEKRA, and Visiopharm, for which UMCG received compensation. Additionally, BvdV is a member of the Palga council, thesaurus, and data minimalization workgroup, for which he has not received any personal fees. No other conflicts of interest were reported by any of the authors.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy restrictions.

ETHICS STATEMENT

All patients in this manuscript have given written informed consent for participation in the study and the use of their deidentified, anonymized, aggregated data and their case details for publication. The TransplantLines cohort study has been assessed and approved by the local ethics committee (Medical Ethical Committee Groningen).

ORCID

Octavian I. Bacoș-Cosma http://orcid.org/0009-0006-2731-4562
Emőke Rácz http://orcid.org/0000-0001-5119-6451

REFERENCES

1. Ulrich C, Kanitakis J, Stockfleth E, Euvrard S. Skin cancer in organ transplant recipients—where do we stand today? Am J Transplant (AJT). 2008;8(11):2192–8.
2. Garrett GL, Blanc PD, Boscardin J, Lloyd AA, Ahmed RL, Anthony T, et al. Incidence of and risk factors for skin cancer in organ transplant recipients in the United States. JAMA Dermatology. 2017;153(3):296–303.
3. Berman H, Shimshak S, Reimer D, Brigham T, Hedges MS, Degesys C, et al. Skin cancer in solid organ transplant recipients: a review for the nondermatologist. Mayo Clin Proc. 2022;97(12):2355–68.
4. Crow LD, Jambusaria-Pahlajani A, Chung CL, Baran DA, Lowenstein SE, Abdelmalek M, et al. Initial skin cancer screening for solid organ transplant recipients in the United States: Delphi method development of expert consensus guidelines. Transpl Int. 2019;32(12):1268–76.
5. Urwin HR, Jones PW, Harden PN, Ramsay HM, Hawley CM, Nicol DL, et al. Predicting risk of nonmelanoma skin cancer and premalignant skin lesions in renal transplant recipients. Transplantation. 2009;87(11):1667–71.
6. Carroll RP, Ramsay HM, Fryer AA, Hawley CM, Nicol DL, Harden PN. Incidence and prediction of nonmelanoma skin cancer post-renal transplantation: a prospective study in Queensland, Australia. Am J Kidney Dis. 2003;41(3):676–83.

7. Lowenstein SE, Garrett G, Toland AE, Jambusaria-Pahlajani A, Asgari MM, Green A, et al. Risk prediction tools for keratinocyte carcinoma after solid organ transplantation: a review of the literature. Br J Dermatol. 2017;177(5):1202–7.
8. Jambusaria-Pahlajani A, Crow LD, Lowenstein S, Garrett GL, Melcher ML, Chan AW, et al. Predicting skin cancer in organ transplant recipients: development of the SUNTRAC screening tool using data from a multicenter cohort study. Transpl Int. 2019;32(12):1259–67.
9. Gómez-Tomás Á, Bouwes BavinckBavinck, JN, Genders R, González-Cruz C, de Jong E, et al. External validation of the Skin and UV Neoplasia Transplant Risk Assessment Calculator (SUNTRAC) in a Large European Solid Organ Transplant Recipient Cohort. JAMA Dermatology. 2023;159(1):29–36.
10. Tanaka T, Voigt MD. Decision tree analysis to stratify risk of de novo non-melanoma skin cancer following liver transplantation. J Cancer Res Clin Oncol. 2018;144(3):607–15.
11. Pothiawala S, Qureshi AA, Li Y, Han J. Obesity and the incidence of skin cancer in US Caucasians. Cancer Causes Control. 2012;23(5):717–26.
12. Gao Y, Twigg AR, Hirose R, Roll GR, Nowacki AS, Maytin EV, et al. Association of HLA antigen mismatch with risk of developing skin cancer after solid-organ transplant. JAMA Dermatology. 2019;155(3):307–14.
13. Bavinck JNB, Vermeer BJ, van der Woude FJ, Vandenbroucke JP, Schreuder GMT, Thorogood J, et al. Relation between skin cancer and HLA antigens in renal-transplant recipients. N Engl J Med. 1991;325(12):843–8.
14. Eisenga MF, Gomes-Neto AW, van Londen M, Ziengs AL, Douwes RM, Stam SP, et al. Rationale and design of TransplantLines: a prospective cohort study and biobank of solid organ transplant recipients. BMJ Open. 2018;8(12):e024502.
15. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc. 1999;94(446):496–509.
16. Wolbers M, Blanche P, Koller MT, Witteman JCM, Gerds TA. Concordance for prognostic models with competing risks. Biostatistics. 2014;15(3):526–39.
17. Blanche P, Kattan MW, Gerds TA. The c-index is not proper for the evaluation of t-year predicted risks. Biostatistics. 2019;20(2):347–57.
18. Breiman L. Classification and regression trees. 1st ed. Routledge; 1984.
19. Wilson S (2021). The MICE algorithm. Available from: https://cran.r-project.org/web/packages/miceRanger/vignettes/miceAlgorithm.html#:~:text=Multiple%20Imputation%20by%20Chained%20Equations%20is%20a%20robust%2C,imputed%20using%20the%20other%20variables%20in%20the%20dataset
20. Gogia R, Binstock M, Hirose R, Boscardin WJ, Chren MM, Arron ST. Fitzpatrick skin phototype is an independent predictor of squamous cell carcinoma risk after solid organ transplantation. J Am Acad Dermatol. 2013;68(4):585–91.
21. Jiyad Z, O'Rourke P, Soyer HP, Green AC. Actinic keratosis-related signs predictive of squamous cell carcinoma in renal transplant recipients: a nested case-control study. Br J Dermatol. 2017;176(4):965–70.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Bacoș-Cosma OI, Sidorenkov GA, Kremer D, Knobbe TJ, Vegt BVD, Bakker SJL, et al. Validity of the skin and UV neoplasia transplant risk assessment calculator (SUNTRAC) tool in a Dutch cohort of transplant recipients. JEADV Clin Pract. 2024;1–10. https://doi.org/10.1002/jvc2.555