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The spectrum of skin diseases in four different types of organ-transplant recipients: a comparative single-centre cohort study

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Background: Organ transplant recipients (OTR) are at marked increased risk of skin cancer and skin infections compared to the general population. *Objectives:* The purpose of this study was to acquire long-term incidence data on commonly occurring skin diseases in four different transplant groups. *Materials & Methods*: This retrospective single-centre cohort study included 621 OTR. By counting defined malignant, inflammatory, infectious or drug-related skin conditions per patient and visit, incidence rates (IR) for the different groups of OTR were calculated as cases per 1000-patient years and cumulative incidences of non-melanoma skin cancer (NMSC), respectively. *Results:* Overall, 2,309 non-malignant skin conditions and 340 NMSC were registered. Skin infections were most common (51.4%), followed by inflammatory skin conditions (35.6%) and sun-induced skin damage (32.9%). Kidney transplant recipients (KTR) had a 4.7-fold (95% CI: 2.7-8.0; $p < 0.0001$), 2.6-fold (95% CI: 1.2-5.3; $p = 0.0098$) and 5.4-fold (95% CI: 2.8-10.3; - < 0.0001) higher IR for oral candidiasis, oral aphthosis and herpes simplex virus infections, respectively, compared to the other OTR. Pruritus was most commonly reported in liver transplant recipients (95% CI: 1.3-5.3; $p = 0.0047$). KTR and lung transplant recipients (LuTR) had a 10.7-fold (95% CI:3.6-43.2; $p < 0.0001$) higher IR of steroid induced acne. KTR had a 1.6-fold (95% CI: 1.1-2.3; $p = 0.0096$) higher IR of squamous cell carcinoma compared to the other groups. The incidence of basal cell carcinoma was 2.5-fold higher (95% CI: 1.7-3.6; $p < 0.0001$) in LuTR, compared to the other OTR. *Conclusion:* This study provides additional organ-specific incidence data on non-malignant skin diseases and skin cancer in OTR.

Key words: organ transplant recipients, skin infections, non-melanoma skin cancer, immunosuppression

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During previous decades, organ transplantation has become a life-saving and frequently performed routine procedure offered to patients with end-stage organ failure. The availability of more efficacious immunosuppressive (IS) treatment has led to an increase in life expectancy. Due to life-long exposure to IS medication, organ transplant recipients (OTR) are prone to malignancies and infections. In particular, it is the carcinogenic nature of the immunosuppressants rather than just the immunosuppressed state of the patients which causes a tremendous risk of skin cancer. Non-melanoma skin cancer (NMSC) accounts for 90% of skin cancer in OTR with squamous cell carcinoma (SCC), representing the majority of NMSC, followed by basal cell carcinoma (BCC). This SCC:BCC ratio, with SCC as the most frequent type of NMSC, is the opposite to that observed in the general, non-immunosuppressed population, in which BCC is more common than SCC [1]. Comparing absolute numbers, OTR have an up to 60-250-fold greater risk of developing SCC than the immunocompetent population [2]. In 10-45% of OTR, skin cancer occurs within 10 years after transplantation [3-6].

IS drugs, usually applied as a combination of steroids, calcineurin inhibitors (CNI) and antimetabolites, impair all components of immunity, including innate and adaptive immunity, leading to compromised immunosurveillance [7]. The IS drug regimen varies between the different types of OTR, which, among other factors, has also served as an explanation for different cumulative incidences of NMSC among the different transplant (TX) populations [8-10]. Generally, the risk of chronic rejection is higher for heart transplant recipients (HTR) and lung transplant recipients (LuTR) requiring higher dosages of IS therapy, which is why these groups are at an increased risk of SCC [1].

Apart from NMSC, OTR have a high burden of various skin diseases, including skin infections and inflammatory as well as IS drug-associated skin conditions. Skin infections may be of bacterial, fungal, or viral origin and occur within a particular time frame after transplantation and the initiation of IS therapy, independent of the organ transplanted [11-13].

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Sustained IS may induce an increased risk of skin infections, which differ according to the post-TX period [14]. In the first post-TX month, bacterial or fungal skin infections occur as an infection of the surgical wound. The fact that opportunistic infections are rarely present in the first post-TX month, when the daily dose of IS therapy is at its highest, emphasizes that the duration of the treatment, *i.e.* the net state of immunosuppression, is the major determinant for this condition [11]. As data on infections of the skin and other non-malignant skin conditions are scarce in OTR, the purpose of our retrospective monocentre study was to acquire long-term incidence data, not only about NMSC but also about the most commonly occurring skin conditions in four different types of OTR. In addition, our intention was to provide information on potential risk factors, such as gender, age, and duration and type of IS therapy.

Patients and methods

In this retrospective study, we included 621 OTR, who had received their transplant at the Medical University of Vienna between May 2000 and November 2013, and had been followed at our dermatology outpatient clinic designated for OTR at the same institution. The patients had either been referred by the TX physicians for their regular, annular skin check or because of prevailing skin problems. At the first visit, demographic data (date of birth, gender, date of transplantation, age at transplantation, type of organ transplanted), the IS regimen and the skin type were assessed. On each visit, a complete dermatological examination was carried out. All visits, procedures and diagnoses including former skin tumours prior and after transplantation, possible risk factors for skin tumours or infections were documented in a dedicated database, comprising data sheets for initial and follow-up visits. Any skin lesion suspicious for NMSC, namely BCC, SCC and Bowen's disease (BD), was either excised at once or biopsied. Actinic keratoses (AK) were either clinically judged or histologically investigated and treated soon after. Patients younger than 18 years of age and patients who had received more than one organ simultaneously and patients with a history of NMSC prior to transplantation were excluded from the analysis.

By counting defined non-malignant, inflammatory, infectious or drug-related skin conditions per patient and visit, the incidence rates (IR) for the different TX groups of various conditions were calculated and expressed as cases per 1000-patient years (p-y). This was only applicable for a subset of skin conditions, where every single episode was counted per patient visit. On the contrary, chronic, persistent skin lesions such as seborrheic warts or onychomycosis were counted only once, calculated for frequency and expressed as percentage share of skin conditions within the total study population.

For the calculation of the different skin conditions, a classification system was created, comprising 13 subgroups which were fungal, viral and bacterial infections, inflammatory and vascular conditions, conditions of the oral mucous membranes, skin conditions due to immunosuppression, benign pigmented and non-pigmented lesions, and conditions of hair and skin appendages, as well as conditions of sun-induced skin damage and so-called miscellaneous skin manifestations. We calculated pruritus as an independent symptomatic skin condition which could not be integrated into one of the defined sub-groups. For NMSC, the cumulative IR were calculated among the different types of OTR. In contrast to precancerous actinic keratosis, consisting of atypical keratinocytes in the basal layers of the epidermis, BD (SCC *in situ*), characterized by full-thickness epidermal atypia, was subsumed under SCC for the calculation of the IR as well as for the SCC: BCC ratio.

Statistical analysis

Metric baseline characteristics were summarized by median and quartiles, and categorical characteristics by absolute and relative frequencies. The frequencies of skin conditions were described based on proportions of affected patients, accompanied by Wilson score confidence intervals. For episodic skin conditions, the incidence was described as number of cases per 1,000-patient years and compared between groups according to incidence rate ratios, accompanied by exact confidence intervals and *p* values. Due to the exploratory nature of the study, no correction for multiple testing was applied. The cumulative incidence of NMSC over time was depicted using the Kaplan-Meier method. The association between age, gender, skin type or type of OTR and risk of NMSC was assessed based on univariable and multivariable complete-case Cox regression models. Proportional hazards assumption was evaluated by plotting the smoothed scaled Schoenfeld residuals and their 95% confidence intervals versus rank of time [15]. Hazard ratios are stated together with Wald confidence intervals. All statistical analyses were performed in SAS (version 9.4, SAS Institute, Inc) and R statistical software (version 3.6.0, R Foundation) with a two-sided significance level of 5%.

Results

Patient characteristics

The baseline characteristics of the cohort are depicted in *table 1*. More than two thirds of the 621 OTR were males (429; 69%). Overall, 268 (43%) were heart transplant recipients (HTR), 71 (11%) liver transplant recipients (LTR), 103 (17%) lung transplant recipients (LuTR) and 179 (29%) kidney transplant recipients (KTR). The median age at TX was 56 years (interquartile range [IQR]: 45-63), with HTR tending to be older than the other OTR. The majority of the patients, for whom Fitzpatrick skin type (FST) was assessed ($n = 470$), were FST II (39%) or III (49%). The median time between TX and last follow-up visit was 3.4 years (IQR: 1.1-6.0) with a median number of two visits (IQR: 1-3).

Most of the patients had a combined IS regime, usually a triple combination therapy, which was the case in 71% of the HTR and LuTR, in 78% of the KTR, but in only 12% of LTR. This regimen contained corticosteroids plus a calcineurin inhibitor (CNI), *i.e.* cyclosporine (CSA) or tacrolimus (TAC) as well as an anti-proliferative drug, *i.e.* mycophenolatmofetil (MMF) or azathioprine (Aza), or a regimen containing a mTOR inhibitor. Ninety-nine percent of the LuTR and 92% of the KTR were receiving a steroid-containing therapy, whereas 71% of the LTR received a steroid-free regimen, usually comprising monotherapy with CNIs.

Table 1. Baseline characteristics of 621 organ transplant recipients.

Patient characteristics	Patients				
	Total (*n* = 621)	**HTR (*n* = 268)**	**LTR (*n* = 71)**	**LuTR (*n* = 103)**	**KTR (*n* = 179)**
Sex, *n* (%)					
Male	429 (69)	213 (79)	53 (75)	50 (49)	113 (63)
Female	192 (31)	55 (21)	18 (25)	53 (51)	66 (37)
First IS regimen (unknown: 36), *n* (%)					
Steroid regimen	469 (80)	204 (79)	19 (29)	94 (99)	152 (92)
Steroid-free regimen	116 (20)	55 (21)	47 (71)	1 (1)	13 (8)
Combination					
Single	36 (6)	2 (1)	31 (47)	0 (0)	3 (2)
Double	158 (27)	73 (28)	26 (39)	25 (26)	34 (21)
Triple	386 (66)	183 (71)	8 (12)	67 (71)	128 (78)
Quadruple	5 (1)	1 (0)	1 (2)	3 (3)	0 (0)
Age at TX, median (IQR), years	56 (45, 63)	57 (47, 63)	57 (51, 64)	52 (35, 60)	55 (41, 66)
Follow-up, median (IQR), years	3.4 (1.1, 6.0)	4.7 (2.6, 8.0)	3.3 (1.2, 5.4)	1.6 (0.9, 4.5)	1.6 (0.3, 4.4)
Number of visits, median (IQR)	2 (1, 3)	3 (2, 5)	1 (1, 2)	1 (1, 2)	1 (1, 2)
Fitzpatrick skin type (unknown: 151), *n* (%)					
FST 1	13 (3)	4 (2)	2 (4)	1 (1)	6 (4)
FST 2	181 (39)	78 (37)	21 (44)	31 (39)	51 (38)
FST 3	229 (49)	115 (55)	19 (40)	40 (51)	55 (41)
FST 4	44 (9)	12 (6)	5 (10)	7 (9)	20 (15)
FST 5	3 (1)	0 (0)	1 (2)	0 (0)	2 (1)

TX: transplantation; IQR: interquartile range; HTR: heart transplant recipients; LTR: liver transplant recipients; LuTR: lung transplant recipients; KTR: kidney transplant recipients; FST: Fitzpatrick skin type; IS regimen: immunosuppressive regimen.

Non-malignant skin conditions

Focusing on the group of skin diseases other than tumours (*table 2*), the most frequently reported diagnoses were skin infections of fungal, bacterial and/or viral origin (319 patients; 51.4%). Confidence intervals (95%) are shown in *table 2*. In 31.6% of the patients, fungal infections of skin and mucous membranes -particularly candidiasis and dermatophyte infections- occurred. Acute episodes of viral skin infection or reactivation were reported in 22.4%. Persistent viral skin infections, such as common or genital warts, were diagnosed in 13.4% of the patients, most frequently in HTR (data not shown). Of the bacterial infections, episodes of bacterial folliculitis, cellulitis, abscesses and phlegmones occurred in 16.3% of the patients. Inflammatory skin diseases were observed in 35.6% of our cohort, comprising, *e.g.* acne vulgaris, dermatitis, or eczema. Clinical signs of sun-induced skin damage were reported in 32.9%, and benign pigmented and non-pigmented lesions in 30.1% and 32.9%, respectively. The oral mucous membranes were affected in 8.7% of the patients by, *e.g.* aphthous lesions, gingivitis or parodontitis, excluding conditions with infectious aetiology. Pruritus was diagnosed in 7.2% of the study population. As side effects of the IS drugs, steroid-induced acne, gingival and sebaceous gland hyperplasia, hypertrichosis and *striae distensae* accounted for 17.7% of the patients. Disorders of hair and skin appendages were diagnosed in 4.4% and vascular conditions, such as varicosis or angiomas, excluding peripheral arterial occlusive disease, in 22.9% of the patients.

For skin conditions for which every single episode was counted, the IR was expressed in cases per 1,000 p-y (*figure 1*). Oral candidiasis occurred 4.7-fold (95% CI. 2.768.0; $p < 0.0001$) more frequently in KTR compared to the other types of OTR (*figure 1A*). The incidence of tinea was 2.8-fold (95% CI: 1.5-5.3; $p = 0.0008$) higher in LTR and KTR than in HTR and LuTR (*figure 1B*), whereas LuTR had a 2.0-fold (95% CI: 0.8-4.5; $p = 0.0787$) higher IR of pityriasis versicolour including pityrosporum folliculitis than the other OTR (*figure. 1C*). The IR for episodes of oral and genital herpes simplex virus manifestations was 5.4-fold (95% CI 2.8, 10.3; $p < 0.0001$) higher in KTR than in the other OTR (*figure 1D*). Interestingly, for herpes zoster, the incidence was comparable between all types of OTR, with the exception of LTR who had a 3.6-fold (95% CI: 0.6-147.7; $p = 0.2494$) lower incidence (*figure 1E*). Bacterial folliculitis occurred more frequently in HTR with an IR of 67 (95% CI: 54-82), compared to the other OTR (*figure 1F*). Acne vulgaris was most frequently diagnosed in LuTR, followed by KTR (*figure 1G*). The IR of eczema was highest in LuTR (*figure 1H*). Differences between the latter three dermatoses were not statistically significant. Pruritus was diagnosed in 15% of all LTR with a 2.7-fold (95% CI: 1.3-5.3; $p = 0.0047$) higher IR compared to the other groups of OTR (*figure 1I*). The incidence of oral aphthosis was 2.6-fold (95% CI: 1.2-5.3; $p = 0.0098$) higher in KTR than in the other TX groups (*figure 1J*). The condition of steroid-induced acne was more frequently diagnosed,10.7-fold (95% CI: 3.6643.2; $p < 0.0001$), in KTR and LuTR (*figure 1K*).

Table 2. Non-malignant skin diseases in 621 organ transplant recipients.

Non-malignant skin disease	Patients *n* (%)						Diseases (*n*)
	Total (*n* = 621)	**Total (95% CI)**	**HTR (*n* = 268)**	**LTR (*n* = 71)**	**LuTR (*n* = 103)**	**KTR (*n* = 179)**	**(*n* = 2309)**
Skin infections	319 (51.4)	47.4, 55.3	156 (58.2)	21 (29.6)	51 (49.5)	91 (50.8)	500
Fungal infections *Tinea versicolor*, dermatomycosis*, onychomycosis, candida balanitis*, pityrosporum folliculitis*, pityriasis versicolor*, candida*: intergluteal, intertrigo, stomatitis, vulvovaginitis, stomatitis, oesophagitis*	196 (31.6)	28.0, 35.3	101 (37.7)	15 (21.1)	22 (21.4)	58 (32.4)	238
Viral infections *Herpes simplex (oral, genital)*, herpes zoster*, mollusca contagiosa*, warts (verruca vulgaris/ plantaris/plana), condylomata acuminata*	139 (22.4)	19.3, 25.8	69 (25.8)	7 (9.9)	20 (19.4)	43 (24.0)	156
Bacterial infections *Folliculitis*, cellulitis*, Impetigo*, abscess*, phlegmon**	101 (16.3)	13.6, 19.4	62 (23.1)	7 (9.9)	12 (11.7)	20 (11.2)	106
Inflammatory conditions *Acne vulgaris*, rosacea, atopic dermatitis, seborrhoic dermatitis*, eczema*, lichen planus**	221 (35.6)	31.9, 39.4	109 (40.7)	26 (36.6)	28 (27.2)	58 (32.4)	306
Pruritus*	45 (7.2)	5.5, 9.6	12 (4.5)	11 (15.5)	10 (9.7)	12 (6.7)	45
Conditions of the oral mucous membranes *Aphtosis minor/major*, gingivitis, parodontitis, lingua geographica*	54 (8.7)	6.7, 11.2	29 (10.8)	2 (2.8)	6 (5.8)	17 (9.5)	56
Skin conditions due to immunosuppressive drugs *Steroid-induced acne*, gingival hyperplasia, hypertrichosis, striae distensae, sebaceus gland hyperplasia**	110 (17.7)	14.9, 20.9	59 (22.0)	6 (8.5)	12 (11.7)	33 (18.4)	123
Benign, pigmented lesions *Café au lait patch, melasma, hyperpigmentation, lentigo simplex, nevi: congenital, Becker*, blue, clark*, dermal*, dysplastic*, junctional*, spilosus*	187 (30.1)	26.6, 33.8	113 (42.2)	15 (21.1)	25 (24.3)	34 (19.0)	244
Benign, non-pigmented lesions *Fibroma, syringoma, dermatofibroma, nevus sebaceus, keloid, lipoma, mucoid cyst*, seborrhoic warts, pigmented purpuric dermatoses, cornu cutaneum*	204 (32.9)	29.3, 36.6	121 (45.2)	25 (35.2)	20 (19.4)	38 (21.2)	257
Conditions of the hair and skin appendages *Effluvium, alopecia*	27 (4.4)	3.0, 6.3	9 (3.4)	0	5 (4.9)	13 (7.3)	28
Vascular conditions *Angiomas, varicosis*	142 (22.9)	19.7, 26.3	85 (31.7)	18 (25.4)	14 (13.6)	25 (14.0)	171
Conditions associated with sun-induced skin damage *Solar lentigo, solary freckling, erythrosis interfollicularis colli, solar elastosis, cutis rhomboidalis nuchae, Favre-Racouchot syndrome, hypomelanosis gutatta*	204 (32.9)	29.3, 36.6	127 (47.4)	14 (19.7)	19 (18.5)	44 (24.6)	291
Others *Skin ulcer*, angioedema*, keratosis pilaris, porokeratosis, stuccokeratosis*, xerosis cutis*	214 (34.5)	30.0, 37.2	92 (34.2)	26 (36.6)	35 (34.0)	61 (34.1)	288

CI: confidence interval.
** Episodic conditions that were registered at each patient visit; other conditions were registered only once.*

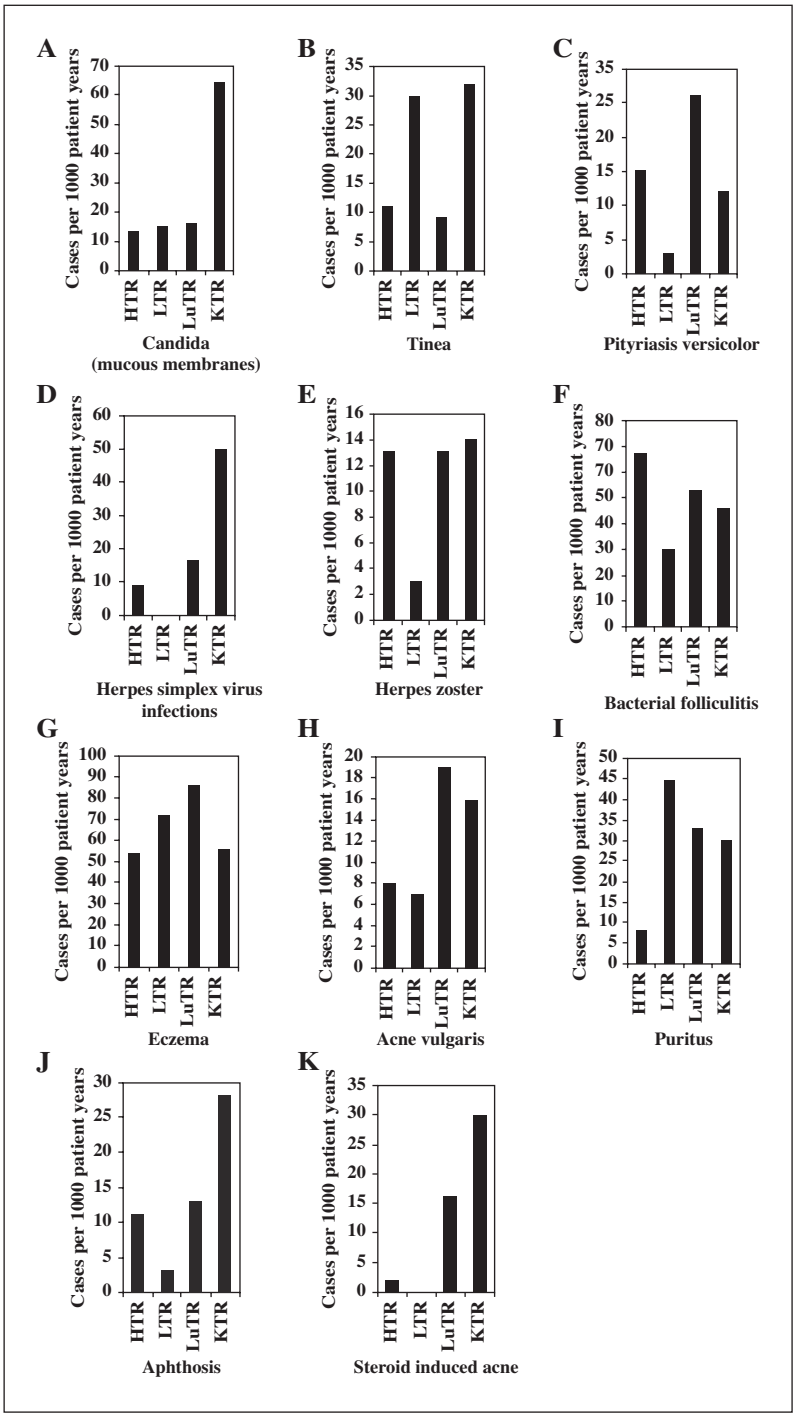

Figure 1. A-**K**) Incidence rates (IR) of episodic non-malignant skin conditions among the four different transplant groups per 1,000 patient years (1000 p-y). **A**) Candida (mucous membranes): IR of 65 (95% CI: 44-92) for KTR; 4.7-fold higher than that in other OTR. **B**) Tinea: IR of 31 (95% CI: 13-60) for LTR and 32 (95% CI: 20-47) for KTR, 2.8-fold higher than that in HTR (IR: 12 [95% CI: 1-19]) and LuTR (IR: 11 [95% CI: 7-18]). **C**) Pityriasis versicolor: IR of 27 (95% CI: 11-52) for LuTR; 2.0-fold higher than that in other OTR. **D**) Herpes simplex virus infections: IR of 51 (95% CI: 33-75) for KTR; 5.4-fold higher than that in other OTR. **E**) Herpes zoster: comparable IR between HTR (IR: 14 [95% CI: 8-21]), LuTR (IR: 13 [95% CI: 4-34]) and KTR (IR: 14 [95% CI: 6-29]); 3.6-fold lower IR (IR: 4 [95% CI: 0.1-21]) in LTR. **F**) Bacterial folliculitis: IR of 67 (95% CI: 54-82) for HTR. **G**) Acne vulgaris: IR of 20 (95% CI: 7-43) for LuTR, and 16 (95% CI: 7-32) for KTR. **H**) Eczema: IR of 86 (95% CI: 56-13) for LuTR. **I**) Pruritus: IR of 46 (95% CI: 24-80) for LTR; 2.7-fold higher than that in other OTR. **J**) Aphthosis: IR of 28 (95% CI 16-48) for KTR; 2.6-fold higher than that in other OTR. **K**) Steroid-induced acne: IR of 30 (95% CI: 17-50) for KTR and 17 (95% CI: 5-39) for LuTR; 10.7-fold higher than that for HTR (IR: 3 [95% CI: 1-7]) and LTR (IR: 0 [95% CI: 0-14]).

Of the OTR receiving a CSA containing IS regimen ($n = 259$), well-known side effects such as sebaceous gland hyperplasia, hypertrichosis and gingival hyperplasia were diagnosed in 19.3% ($n = 50$), 3.9% ($n = 10$) and 4.6% ($n = 12$) of the patients, respectively. In 16.0% ($n = 85$) of the OTR on CNI, episodes of seborrheic dermatitis occurred. For patients who were on steroids ($n = 469$), conditions such as folliculitis, steroid-induced acne and oral candidiasis were reported in 17.3% ($n = 81$), 3.4% ($n = 16$) and 9.8% ($n = 46$), respectively (data not shown).

For skin conditions possibly associated with the intake of particular IS drugs, for which every episode was registered, the IR per 1,000 p-y between patients, with and without a certain IS drug, was compared (*figure 2*). Considering folliculitis and acne, the IR was 2.4-fold (95% CI: 1.464.6; $p = 0.0006$) (*figure 2A*) and 2.7-fold (95% CI: 0.6623.5; $p = 0.2910$) (*figure 2B*) higher in OTR receiving steroids than OTR with a steroid-free IS regimen, respectively. The incidence of candidiasis of the skin and the mucous membranes was very similar for patients with and without steroids (*figure 2C*). Furthermore, in patients receiving CNI, the IR of seborrheic dermatitis was 1.9-fold (95% CI: 0.964.8; $p = 0.1071$) higher than in patients without CNI (*figure 2D*).

Malignant skin lesions

Focusing on the group of malignant and premalignant skin lesions in our cohort (*table 3*), there was a total of 325 histologically confirmed post-TX NMSC in 103 of the 621 OTR (16.6%), with a larger proportion of NMSC in male than female patients (18.4% versus 12.5%). Forty-one patients had only a single NMSC, 62 patients developed more than one (44 OTR had two to five skin malignancies, 18 OTR more than five). SCC was diagnosed in 10.5%, Bowen's disease (SCC *in situ*) in 5.5% and BCC in 11.4% of the OTR, respectively, corresponding to a SCC: BCC ratio almost equal to one.

Premalignant lesions, namely AK and actinic cheilitis, were diagnosed in 15.3% ($n = 95$) of all OTR. In 56.9% of the patients with SCC, AK was concomitantly present. A melanoma was diagnosed in 11 patients (1.8%). Eleven OTR had a post-TX melanoma, which had occurred within a mean time of 8.6 years after TX (range: 1.3-27.8 years). Superficial spreading melanoma (SSM) represented the most frequent histopathological subtype ($n = 5$; 45%), followed by melanoma not specifically classified ($n = 3$; 27%), lentigo maligna melanoma (LMM) ($n = 2$, 18%), and nodular melanoma (NM) ($n = 1$; 10%). According to the current AJCC staging system [16], 45% ($n = 5$) of OTR were diagnosed with melanoma *in situ*; melanoma Stage IA in 36% ($n = 4$) and melanoma Stage IB in 18% ($n = 2$).

Kaposi sarcoma occurred in two KTR, and a cutaneous lymphoma was diagnosed only once in a HTR.

The IR per 1,000 p-y for the different types of skin cancers in the different TX groups are shown in *figure 3*. The IR for NMSC in general was highest in LuTR (IR: 205; 95% CI: 158-263) (*figure 3A*), and that for BCC was also higher, by 2.5-fold (95% CI: 1.7-3.6; $p < 0.0001$), compared to the other OTR. (*figure 3B*). Squamous cell carcinoma was more frequently diagnosed, 1.6-fold (95% CI: 1.1-2.3; $p = 0.0096$), in KTR compared to the other OTR (*figure 3C*). The IR of melanoma was 1.9-fold (95% CI: 0.47-7.59; $p = 0.3247$) higher in LTR and KTR than in HTR and LuTR (*figure 3D*).

The median time from TX to the first NMSC diagnosis was 12.0 years (IQR: 6.5; not estimable). The cumulative IR (CIR) for NMSC calculated for the whole study population increased from 10% after 2.5 years to 20.5% after five, and 36.2% after 10 years (data not shown). When the different TX groups were compared, the CIR was highest after five years in LuTR (28.0%), but without statistical significance compared to the other OTR ($p = 0.0852$) (*figure 4*).

Based on the multivariable Cox regression analysis, taking into account age at TX, gender, skin type and type of OTR, the risk factors, older age at TX (HR: 2.3 per decade; 95% CI: 1.7-3.0; $p < 0.0001$) and light skin type (HR: 0.6; 95% CI: 0.4, 0.8; $p = 0.0048$), were significantly associated with an increased risk of NMSC. The adjusted hazard ratio for NMSC was 1.2-fold (95% CI: 0.7-2.2) higher for KTR than for HTR, 1.7-fold (95% CI: 0.8-3.6) higher for LuTR than for HTR, and approximately the same (HR: 1; 95% CI: 0.8-3.6) for LTR and HTR (data not shown).

Discussion

OTR are prone to a plethora of malignant and non-malignant skin conditions. Thorough expertise in the diagnosis and

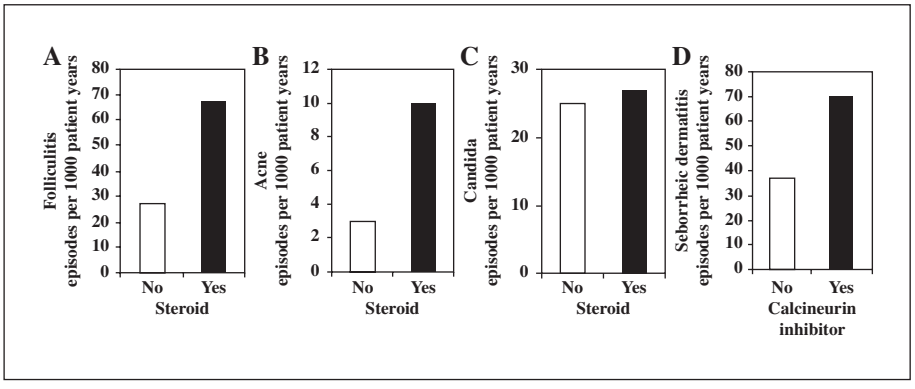

Figure 2. **A**-**D**) Incidence rates per 1,000 patient years (p-y) for skin conditions possibly associated with intake of particular IS drugs within the whole cohort of OTR. **A**) Folliculitis and steroids. **B**) Acne and steroids. **C**) Candida and steroids. **D**) Seborrheic dermatitis and calcineurin inhibitor.

Table 3. Malignant skin lesions.

Skin tumours	Patients (*n*) (%)					Lesions (*n*)
	Total (*n*=621)	HTR (*n*=268)	LTR (*n*=71)	LuTR (*n*=103)	KTR (*n*=179)	
Premalignant lesions						
Total	95 (15.3)	55 (20.5)	8 (11.3)	11 (10.7)	21 (11.7)	158
Actinic keratosis	93 (15.0)	55 (20.5)	8 (11.3)	10 (9.7)	20 (11.2)	141
Actinic cheilitis	14 (2.3)	8 (3.0)	1 (1.4)	2 (1.9)	3 (1.7)	17
Malignant lesions						
NMSC	103 (16.6)	48 (17.9)	12 (16.9)	17 (16.5)	26 (14.5)	325
BCC	71 (11.4)	32 (11.9)	11 (15.5)	11 (10.7)	17 (9.5)	165
Bowen's disease	34 (5.5)	13 (4.9)	4 (5.6)	2 (1.9)	15 (8.5)	60
SCC	65 (10.5)	30 (11.2)	4 (5.6)	11 (10.7)	20 (11.2)	100
Combined with AK	37 (6.0)	19 (7.1)	3 (4.2)	4 (3.9)	11 (6.2)	
Melanoma	11 (1.8)	5 (1.9)	2 (2.8)	1 (1.0)	3 (1.7)	11
Kaposi sarcoma	2 (0.3)	0	0	0	2 (1.1)	2
Lymphoma	1 (0.2)	1 (0.4)	0	0	0	1

NMSC: non-melanoma skin cancer; BCC: basal cell carcinoma; SCC: squamous cell carcinoma; AK: actinic keratosis.

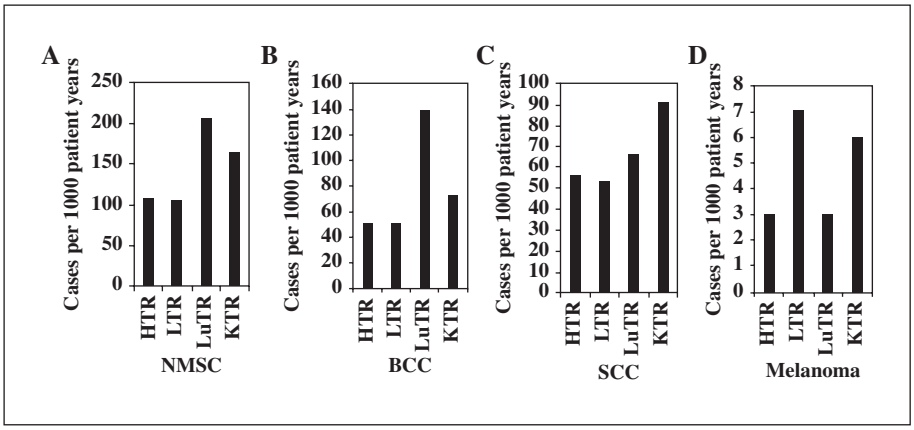

Figure 3. A-**D**) Incidence rates per 1,000 patient years (p-y) of malignant skin conditions among the four different transplant groups. **A**) NMSC: IR of 205 (95% CI: 158-263) for LuTR. **B**) BCC: IR of 139 (95% CI: 100-188) for LuTR; 2.5-fold higher than that in other OTR. **C**) SCC: IR of 91 (95% CI: 67-122) for KTR; 1.6-fold higher than that in other OTR. **D**) Melanoma: IR of 8 (95% CI: 0.9-27.6) for LTR and 6 (95% CI: 1.3-17.8) for KTR; 1.9-fold higher than that in HTR (IR: 4 [95% CI: 1.1-8.1]) and LuTR: (IR: 3 [95% CI: 0.1-18.5]).

management of these diseases within a designated dermatologic clinic for OTR is of pivotal importance in order to meet the needs of these patients and to ensure education, prevention and early intervention [17]. Facing the abundance of information on cutaneous neoplasms in OTR, data on non-malignant skin conditions among these patients are under-represented in the literature, despite the fact that many patients develop multiple or recurrent skin diseases. However, it is difficult to draw conclusions whether particular skin conditions are TX-related or not. It is also difficult, if not even impossible, to estimate, whether their occurrence and distribution within the transplant population simply represent what is seen in an age- and gender-matched collective of patients. An approach to face this situation is to investigate the prevalence as well as comparative incidence data of skin diseases and their spectrum in different groups of OTR.

In our study, for the first time, a large variety of skin conditions, corresponding to four different types of OTR, were assessed in an equal setting of an established specialised clinic, and their relative contributions to the morbidities in this population were analysed in a comparative study. Skin infection accounted for 51.4% our cohort, which confirms data from former studies that skin infections, either of fungal, viral or bacterial origin, are the most commonly recorded diagnoses in OTR, particularly in the early post-TX period [13, 14, 18, 19]. In our population, the occurrence of skin infections was followed by inflammatory skin conditions (35.6%), clinical signs of sun-induced skin damage (32.9%) and benign pigmented and non-pigmented lesions (30.1% and 32.9%, respectively).

Skin infections were most frequently due to fungal pathogens, consisting of *Candida* spp., *Malassezia furfur* and dermatophyte infections, affecting 31.6% of our patients. Infections due to dermatophytes, which also included onychomycosis, represented the majority, affecting 24% of the OTR, followed by candidiasis (9% of the OTR) and infections with *Malassezia furfur* (5% of the

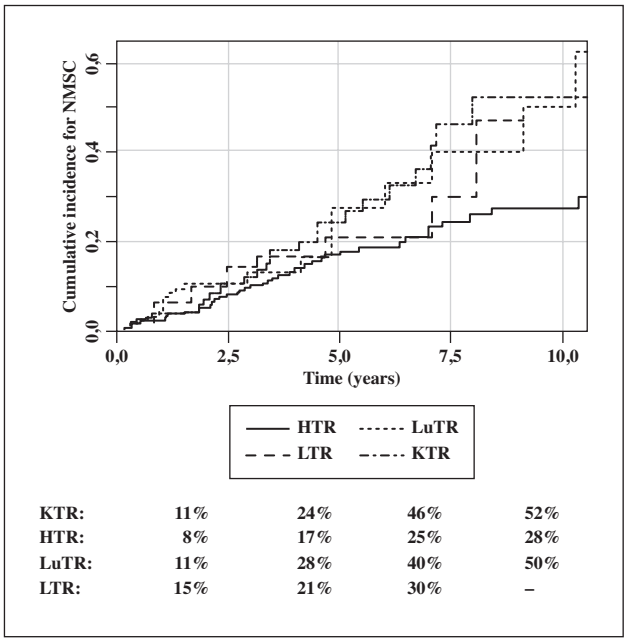

Figure 4. Cumulative incidence rates of NMSC in 621 organ transplant recipients, stratified for the different types of OTR.

OTR). Generally, OTR are prone to the development of candidiasis of the mucous membranes, mostly due to *Candida albicans*, but also non-albicans *Candida* spp. These patients are also known to have higher rates of colonization compared to the general population [20]. In the literature, the prevalence of oral candidiasis, *e.g.* in KTR, was reported to range between 7.7% and 25.5% [21, 22]. In our cohort, KTR demonstrated a 4.7-fold higher prevalence of oral candidiasis compared to the other OTR, which was statistically significant. Whether there is a causal connection with a particular IS regimen in this TX group can only be speculated. In one of the largest prospective case control studies on 400 OTR, no significant difference regarding an association between colonization or mucositis due to *Candida* spp. and a particular TX group was observed. Although not significant, higher dosages of corticosteroids and tacrolimus correlated with symptomatic candidiasis in this study [20]. Interestingly, Spolidorio and co-workers reported on KTR receiving a CSA-based IS regimen with higher salivary levels of *Candida* spp. compared to patients on tacrolimus [23].

In our population, *pityriasis versicolor* was more commonly diagnosed in LuTR, and rarely seen in *e.g.* LTR, who usually have a mono IS regimen without steroids. *Malassezia furfur,* an opportunist like *Candida* spp., causes colonization and may lead to pityrosporum folliculitis or superficial skin infection under immunosuppression, which has been observed in up to 36% of KTR [24]. The higher prevalence *of pityriasis versicolor* in our LuTR may be attributed to the higher dosages of IS and the steroid-containing regimen in 91% of these patients. In a case control study on KTR compared to healthy controls, Gülec and co-workers revealed CSA and TAC intake as independent risk factors for the development of this skin condition [22].

Reactivation of human herpesviruses, mainly herpes simplex viruses (HSV) and varicella zoster virus (VZV), are common in the post-TX period [14] and typically occur within the first months after transplantation [11]. In our cohort, the incidence of HSV associated manifestations was significantly higher (5.4-fold) in KTR than in the other OTR. We have no explanation for this finding. The IS monotherapy in LTR may serve as an explanation for the lowest IR of herpes zoster in our study. According to published data, the prevalence of HZ in OTR varies from 1.5% to 16.2%, which was attributed to variations in the type of IS regimen and antiviral prophylaxis [25-27]. In another study, in accordance with our results, LTR demonstrated a lower incidence of HZ than LuTR and KTR [28]. A large retrospective multicentre cohort study on the incidence of HZ in more than 1,000 OTR reported an IR of 22.2 per 1,000 p-y and was highest in African American OTR and HTR [29]. The IR of HZ in our cohort of HTR was lower, namely 13 per 1000 p-y.

In our cohort, HTR showed the highest IR of bacterial folliculitis, followed by LuTR, KTR and LTR, which may be attributed to the different, decreasing levels of IS in OTR [14]. We tried to clearly distinguish this condition from "acne", which is used for pustular follicular-bound lesions. In contrast to folliculitis, acne typically appears in younger patients, predominantly on the face and upper trunk. Acneiform eruptions due to corticosteroid therapy are also difficult to distinguish. Clinically, steroid-induced acne is described with specific features, namely a monomorphic pattern, an unusual location of the lesions beyond the seborrheic areas, an unusual age at onset, resistance to conventional acne therapy and, of course, the notion of recent introduction of steroids [30]. This condition has also been associated with abundant *Malassezia* spore loads in OTR [31]. In our study population, KTR and LuTR had a 10.7-fold higher IR of steroid-induced acne than HTR and LTR, which was statistically significant. This condition was not present in LTR, who mainly received a steroid-free IS regimen.

In our study, 17.7% of skin diseases were attributed to IS drugs other than steroids, and most importantly, the intake of CNIs may lead to gingival hyperplasia, hypertrichosis, sebaceous gland hyperplasia or seborrheic dermatitis; the latter was 1.9-fold more frequently diagnosed in patients receiving a CNI-containing IS regime. Apart from this, and consistent with published data, seborrheic dermatitis was the most common inflammatory skin condition observed in 32% of our patients [32, 33].

Due to the lack of clinical correlation, "pruritus" was analysed separately, and interestingly, was significantly more frequently present in LTR, a well-known fact in this subgroup of OTR [34]. According to the literature, in LTR, pruritus can either be attributed to cholestasis caused by anastomosis or due to other factors that account for the impairment of bile flow, or may also represent a sign of chronic ductopenic graft rejection [35].

We also registered the condition, aphthous lesions of the oral mucosa, which was importantly discriminated from manifestations due to viral infection based on clinical appearance and a negative PCR result. This condition was observed in 4.7% of our patients with a significant 2.6-fold increased incidence in KTR. We have no explanation for this observation. This could possibly be drug related. In the literature, aphthous lesions appear to be more frequent in KTR treated with CsA compared to tacrolimus [23]. An association with intake of mTOR inhibitors is well known, but it is also reported in connection with MMF [36]. However,

in our cohort, we could not find any significant correlation with mTOR inhibitors, mainly due to the low number of patients on an mTOR-containing IS regimen.
A total of 325 NMSC were excised in our patients in the observation period. The driving power for the development of NMSC is ultraviolet (UV) damage, in particular, UVB light causing direct DNA damage of keratinocytes and initiating carcinogenesis [37]. This is why patients of older age at transplantation are more prone to develop NMSC [38-40]. In accordance with the literature, this factor was also found to be significantly associated with the occurrence of NMSC in our study population, as well as a light skin type.
Another key point in NMSC development in OTR is the carcinogenic potential of immunosuppressants to cause DNA damage depending on the type, level and duration of the medication. Thus, OTR requiring higher dosages of IS therapy (such as LuTR and HTR) are at higher risk of NMSC [1]. In 56.9% of our patients with SCC, AK were diagnosed which are reportedly predictive of SCC development within a period of 18 months [41].
Furthermore, it is well known that the IR of post-TX NMSC differs according to geographic latitude, which also reflects the influence of UV exposure. In the Austrian TX population described in the present study, the cumulative incidence rate for all different types of TX patients taken together was 10% after 2.5 years, 20.5% after five, and 36.2% after 10 years. These results are higher than those reported from Germany, which is more northerly [42]. Further studies on the cumulative incidence of NMSC in different geographical regions exist for particular types of TX patients, mainly KTR. KTR from the Netherlands, a region of limited sun exposure, had lower CIR after 10 and 20 years (10% and 40%, respectively), compared to Australian KTR with rates of 45% and 70% after the same period of time [43, 44]. However, this escalation is even more pronounced in HTR. In Australia, an increase in 34.5% was reported between the fifth (8.5%) and tenth year (43%) after heart transplantation. Accordingly, the incidence data from a retrospective analysis of Austrian HTR [10] was higher than that reported in Scandinavia [45] and slightly lower than that in Italy [46]. Interestingly, in our study, although not significant when compared to the other groups of OTR, the cumulative incidence of NMSC was highest in LuTR, with a CIR of 28% after five years. Comparable numbers after this time period, namely CIR of 31% and 26%, have been reported in single-centre studies on LuTR [38, 47].
When the different TX groups are compared according to IR per 1,000 p-y of NMSC, LuTR reveal the highest IR, which is in accordance with the literature, with HTR or LuTR reportedly having higher IR of NMSC than KTR and LTR [48]. Older age at transplantation, male gender and greater immunosuppression in these patients served as an explanation for this difference [49]. Furthermore, KTR have been shown to have at least a two-fold reduced risk of developing NMSC compared to HTR [8, 9, 50].
Regarding the different types of NMSC, KTR had a 1.6-fold higher IR of SCC and LuTR a 2.5-fold higher IR of BCC compared to the other groups, which were both significant. In LuTR, the treatment with voriconazole against severe fungal infections may serve as an explanation for this observation, as its metabolite, voriconazole N-oxide, promotes phototoxicity [51, 52]. However, in a recent report, only the occurrence of SCC, but not BCC, was significantly associated with previous voriconazole treatment. Another single-centre, retrospective cohort study on LuTR emphasized that the duration of voriconazole intake was an independent risk factor for NMSC development after lung transplantation, but there was no discrimination between SCC or BCC [53].
Finally, as a reflection of the particularly higher risk of SCC compared to BCC in OTR, the SCC:BCC ratio ranges between 1:1 and 2:1, which is in contrast to the ratio of 1:4 in the general population. Therefore a SCC:BCC ratio almost equal to one in our study is in accordance with the literature [4, 9].
A limitation of our study is the retrospective design, which is also linked to limited access to data on IS therapy modification over time. Furthermore, the various skin conditions may have been underestimated, as patients may have been seen additionally in other institutions.
In conclusion, large cohort studies on non-malignant and malignant skin diseases in all groups of OTR are rare, however, these are of importance as they highlight the different risk profiles for particular skin conditions in these patients. Careful dermatological screening and long-term follow-up are essential for early detection and therapy of skin diseases in OTR. ■

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