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The association between immunosuppression and skin cancer in solid organ transplant recipients: a control-matched cohort study of 2,852 patients

Background: Skin cancer is more common in transplant recipients, although the quoted incidence is variable. *Objectives:* This study investigated the incidence of skin cancer in solid organ transplant recipients (OTRs) in a national cohort and the effect of pharmacotherapeutic agents *Materials & Methods:* Transplant patients were identified from Patient Episode Database for Wales (PEDW) using Office of Population Census and Surveys Classifications of Interventions and Procedures-4 (OPCS-4) codes. Controls were matched to cases according to age, sex and socioeconomic status. Skin cancer data were obtained from linkage with other national data sources. Incidence was calculated per 100,000 person-years at risk (PYAR). Negative binomial regression was used to calculate adjusted incidence rate ratios (IRRs) for each organ type. *Results:* During 2000-2018, 2,852 Welsh patients underwent solid organ transplantation. A total of 13,527 controls were matched from the general population. The incidence of skin cancer within the OTR cohort was 1203.2 per 100,000 PYAR vs 133.9 in the matched control group. Age, male gender and azathioprine use were all associated with an increased risk of skin cancer. Contemporary immunomodulators such as tacrolimus and mycophenolate were associated with a reduction in skin cancer risk when compared to their predecessors, cyclosporin and azathioprine. The highest adjusted IRR was observed in heart transplant recipients (IRR: 10.82; 95% CI: 3.64-32.19) and the lowest in liver transplant recipients (IRR: 2.86; 95% CI: 1.15-7.13). *Conclusion:* This study highlights the need for long-term routine skin cancer surveillance for all OTRs and the importance of using contemporary immunomodulators, when possible, for risk reduction.

Key words: skin cancer, immunosuppression, transplant, oncology

Skin cancer is the most common malignancy in organ transplant recipients (OTRs) [1]. Previous studies have estimated the risk of skin cancer in OTRs to be 10 to 250 times greater than that of the general population [2, 3]. In addition to the increased incidence, squamous cell carcinomas in OTRs are significantly more likely to be multiple, more locally invasive, involve perineural and lymphatic invasion, have higher recurrence rates, and require radiation or chemotherapy [4, 5].

In addition to cumulative UV exposure, previous studies have identified sex, age at transplantation, the type of organ transplanted and the immunosuppressive regime as risk factors for developing skin cancer [6-8]. The higher morbidity and mortality in this group of patients has triggered interest in the differences in tumourigenic potential between immunosuppressants used for maintenance therapy.

Contemporary maintenance immunosuppression employs a triple drug regime consisting of a calcineurin inhibitor (CNI) (cyclosporin or tacrolimus), an anti-proliferative agent (mycophenolate, azathioprine) and a steroid (*figure 1*) [9, 10]. More recently, mammalian target of rapamycin (mTOR) inhibitors, such as everolimus and sirolimus, have been introduced as alternatives to CNIs, which are associated with nephrotoxicity and increased cardiovascular disease [11].

Whilst the increased risk of skin cancer is well recognised, skin specific surveillance guidance for transplant centres exists only for renal transplants [12]. In our previous work, 45% organ transplant centres across the United Kingdom did not perform routine surveillance. Lack of funding, inadequate training and time restraints were the most frequent barriers described for not providing screening [13].

Previous studies investigating risk factors for skin cancer of OTR patients have been limited by focusing on regional data, one organ type, the lack of a control group, limited

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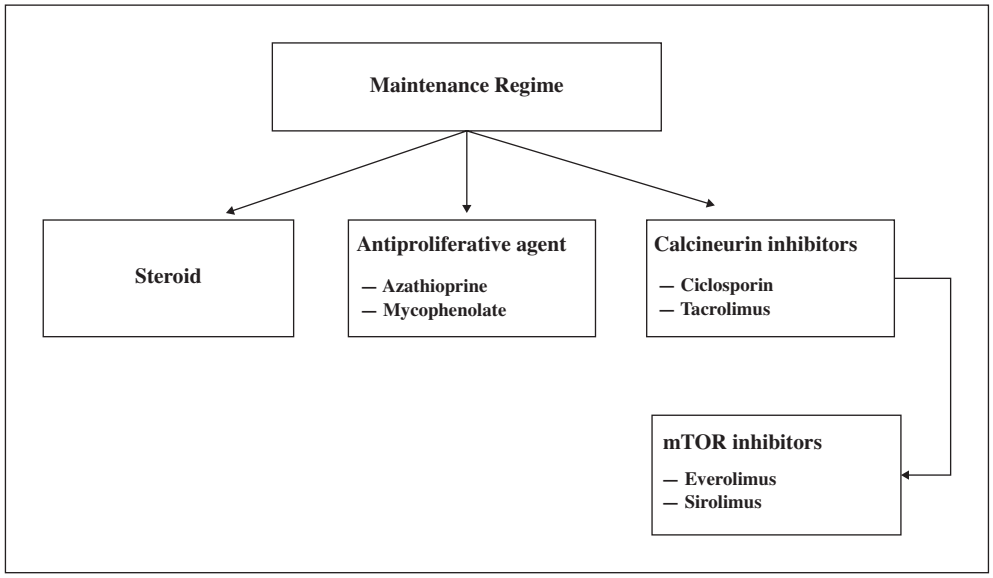

Figure 1. Maintenance regimes.

detail on the immunosuppressive regime and the use of surveillance systems with incomplete registration of skin cancer [2, 14-16]. The aim of our study was to provide a total population overview of the epidemiology of skin cancer amongst OTRs in order to provide an evidence base to inform policy makers of the need for skin cancer surveillance.

Methods

Design

In this population-based cohort study, analysis of primary and secondary care National Health Service (NHS) data and national administrative data for 2000-2018 in Wales, UK (population 3.1 million) were performed. In Wales, population level de-identified person-based health and socio-economic administrative data are collated and linked within the Secure Anonymised Information Linkage (SAIL) Databank [17-19]. This study has been designed and reported in accordance with the Reporting of studies Conducted using Observational Routinely-collected health Data (RECORD) statement [20] (*supplementary table 1*). The list of data sources used and their description is presented in *table 1*.

Cohort

Cases

OTRs were identified from Patient Episode Database for Wales (PEDW) using Office of Population Censuses and Surveys Classification of Interventions and Procedures (OPCS-4) procedural codes for organ transplantation (*supplementary table 2*) between 1st January 2000 and 31st December 2018. Participants entered the study at the time of transplantation and were followed until the development of a skin cancer, death or up to 31st December 2018. Details on the prescription and duration of immunosuppressive

Table 1. List of data sources used and their description.

Database	Description
Annual District Death Extract (ADDE)	Collected from the Office for National Statistics (ONS), containing death registration information, relating to Welsh residents including those who died outside of Wales.
Outpatient Dataset for Wales (OPDW)	Administrative and clinical data obtained from outpatient appointments in Wales.
Patient Episode Database for Wales (PEDW)	Administrative and clinical data for all hospital admissions, including diagnosis and operations performed.
Welsh Cancer Intelligence and Surveillance Unit (WCISU)	The national cancer registry for Wales. Captures all Welsh melanoma patients from a number of sources; multi-disciplinary team data, pathology data, other routine data sources in Wales and the English cancer registry.
Welsh Longitudinal General Practice dataset (WLGP)	Administrative and clinical data from all patient visits to a general practitioner.
Welsh Demographic Service Dataset (WDSD)	Administrative data about individual's resident or registered in Wales that have used National Health Service (NHS) services.

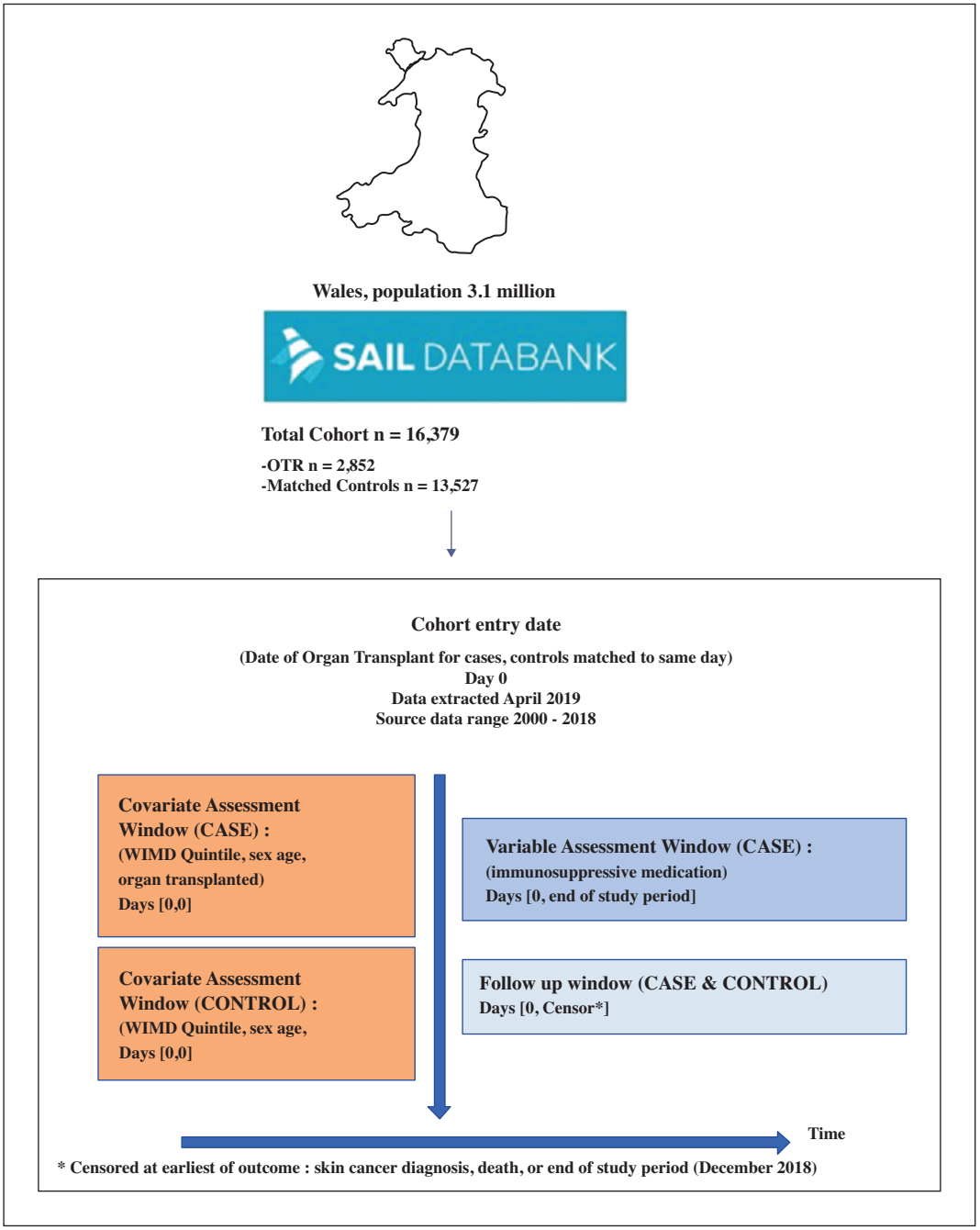

Figure 2. Study design.

medication were obtained from primary care data (Welsh Longitudinal General Practice [WLGP]) (*supplementary table 3*).

Controls

Healthy controls were selected from the Welsh Demographic Service Dataset (WDSD) and matched to cases by age at transplantation, socioeconomic status (WIMD) and sex. Controls were excluded if they were on immunosuppressive medication as identified from their GP record. To improve the power of the study, we aimed to have five controls per case [21]. Controls entered the study at the time of their respective matched-case transplantation and were followed until the development of a skin cancer, death or up to 31st December 2018.

Outcome

The primary outcome of the study was the development of a melanoma or non-melanoma skin cancer (NMSC). Melanoma diagnosis was established based on the Welsh Cancer Intelligence and Surveillance Unit (WCISU) register, where recording of melanoma is compulsory, using International Classification of Disease version 10 (ICD 10) codes (*supplementary table 4*). Hospital episode statistics

Table 2. OTR demographics per organ transplanted.

	Kidney (*n* = 2102)	Pancreas (*n* = 76)	Heart (*n* = 100)	Lung (*n* = 129)	Liver (*n* = 437)	*p* value
Median age, y (IQR)	48.0 (36.4-59.8)	41.1 (35.8-45.7)	43.7 (26.0-53.7)	49.7 (34.3-57.8)	52.7 (39.6-59.8)	0.00
Age (y), *n* (%)						
0-9	40 (1.9)	0 (0.0)	8 (8)	0 (0.0)	31 (7.1)	
10-19	104 (4.9)	<5*	12 (12)	7 (5.4)	18 (4.1)	
20-29	196 (9.3)	7 (10.0)	11 (11)	16 (12.4)	28 (6.4)	
30-39	311 (14.8)	25 (32.9)	12 (12)	17 (13.2)	34 (7.8)	
40-49	448 (21.3)	33 (43.4)	25 (25)	26 (20.2)	75 (17.2)	
50-59	492 (23.4)	10 (13.2)	20 (20)	46 (35.7)	146 (33.4)	
60-69	361 (17.2)	0 (0.0)	12 (12)	17 (13.2)	100 (22.9)	
≥70	150 (7.1)	0 (0.0)	0 (0.0)	0 (0.0)	5 (1.1)	
Gender, *n* (%)						
Male	1370 (65.2)	30 (39.5)	69 (69)	66 (51.2)	274 (62.7)	0.00
Female	732 (34.8)	46 (60.5)	31 (31)	63 (48.8)	163 (37.3)	
WIMD Quintile, *n* (%)						
1	465 (22.1)	19 (25.0)	17 (17)	27 (20.9)	93 (21.3)	0.80
2	428 (20.4)	15 (19.7)	21 (21)	33 (25.6)	86 (19.7)	
3	386 (18.4)	12 (15.8)	20 (20)	26 (20.2)	88 (20.1)	
4	384 (18.3)	13 (17.1)	16 (16)	16 (12.4)	72 (16.5)	
5	363 (17.3)	13 (17.1)	20 (20)	20 (15.5)	76 (17.4)	
Unspecified	76 (3.6)	<5*	6 (6)	7 (5.4)	22 (5.0)	
Skin cancer after transplant, *n* (%)						
N	195 (9.3)	<5*	9 (9)	<5*	19 (4.3)	0.01
MSC: Melanoma	9 (0.4)	<5*	0 (0.0)	<5*	<5*	
None	1898 (90.3)	72 (94.7)	91 (91)	124 (96.1)	417 (95.4)	
Median time to skin cancer development, years (IQR)	4.60 (2.37-7.50)	4.52 (6.45-7.48)	8.50 (2.52-11.57)	5.47 (4.68-5.55)	4.76 (2.82-6.88)	
Immunosuppression data, *n* (%)	1638 (77.9)	63 (83.0)	69 (96.0)	96 (74.4)	324 (74.1)	
Immunosuppression treatment, *n* (%)						
Steroid	1274 (77.8)	37 (58.7)	62 (90.0)	95 (99.0)	232 (71.6)	0.00
Cyclosporin	270 (16.5)	12 (19.0)	28 (40.6)	47 (49.0)	24 (7.40)	0.00
Tacrolimus	1097 (67.0)	51 (81.0)	26 (37.7)	46 (47.9)	281 (64.3)	0.00
Azathioprine	419 (25.6)	16 (25.4)	19 (30.2)	53 (41.1)	163 (50.3)	0.00
Mycophenolate	1001 (61.1)	46 (73.0)	42 (66.7)	48 (50.0)	124 (38.3)	0.09
Sirolimus	129 (7.9)	6 (9.5)	<5*	<5*	16 (4.9)	1.00
Everolimus	<5*	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1.00
Belatacept	0 (0.0)	0 (0.0)	0 (0.0)	<5*	0 (0.0)	

**Results based on <five individuals are not released from SAIL via disclosure control policies, to ensure privacy protection adherence.*

(obtained from PEDW) and outpatient data (obtained from the Outpatient Dataset for Wales [OPDW]) were used in addition to WCISU to identify a diagnosis of NMSC. Registration of NMSC in the WCISU has only been compulsory from 2016.

Ethical approval

Study approval was granted by the SAIL Databank independent Information Governance Review Panel (IGRP) (Project 0792). Data held within the SAIL Databank are made available to researchers in an anonymised format and are therefore not subject to data protection legislation. SAIL uses population data for research and follows all relevant legislative and regulatory frameworks.

Statistical analysis

Descriptive statistics were used to provide overall characteristics of the OTR cohort. The incidence of skin cancer within the cohort was expressed per 100,000 person-years at risk (PYAR). Kaplan-Meier curves were generated to estimate the cumulative risk of skin cancer by organ type.

To determine the risk of skin cancer in OTRs compared to the control group, incidence rate ratios (IRRs) were calculated using a multivariate negative binomial regression model to account for differential follow-up. Age at cohort entry (as a continuous variable), sex, immunosuppressive medication and socioeconomic status were included in the model. Socioeconomic status was measured using the Welsh Index of Multiple Deprivation (WIMD) version 2004; a measure based on the Index of Multiple Deprivation and used as the official measure of socioeconomic status by the Welsh Government [22]. Patients were assigned to one of five quintiles based on their postal code, with Quintile 1 being the lowest socioeconomic status and 5 being the highest.

Immunosuppressive medications were analysed according to whether a patient had taken a medication for longer than one month. We performed detailed subgroup

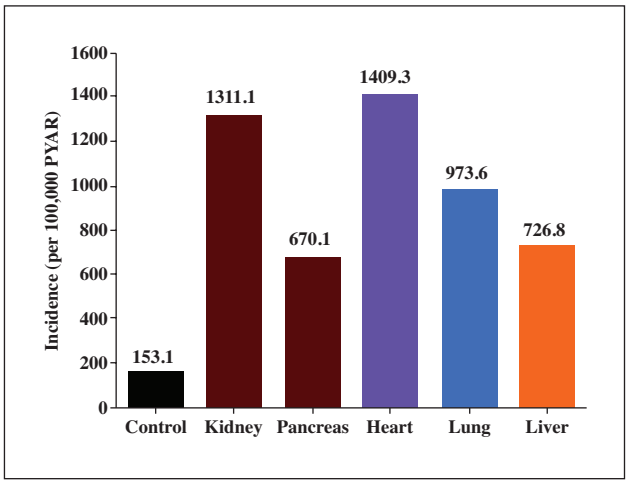

Figure 3. Incidence of skin cancer according to type of organ transplant (per 100,000 PYAR).

analysis comparing the risk profile of medications between different regimes and within the same drug category; CNI (tacrolimus and cyclosporin) and antiproliferative agents (mycophenolate and azathioprine).

We included all individuals who had complete data for all variables in the study. All data were analysed using IBM SPSS Statistics for Windows (IBM Corp. Released 2017. Version 25.0. Armonk, NY: IBM Corp). Statistical significance was assumed with a $p < 0.05$. Prism 6 (Graphpad Software, San Diego) was used for graphing. An overview of the study is displayed in *figure 2*.

Results

Demographics

Between 1st January 2010 and 31st December 2018, 2,852 patients were identified as OTRs with 20,113 total person-years of follow-up (*table 2*). The median follow-up time was 6.2 years (IQR: 3.0-10.5 years). Immunosuppression medication data were available for 2,190 (76.7%) patients. The most common organ transplanted was the kidney (73.7%). There were six records for combined heart and lung transplantation and <five records for small intestinal transplantation. Results referring to less than five individuals are not released from SAIL due to disclosure control policies to ensure privacy protection. Therefore, these patients were excluded from analysis.

The predominant subgroup of skin cancer developed by the cohort was NMSC (95%). The median time to develop skin cancer from the time of transplantation was 4.7 years (IQR: 4.7-7.5 years).

Controls

A total of 13,527 controls were matched to the OTR cohort, contributing to 114,302.6 person-years of follow-up (*supplementary table 5*).

Incidence

Among the OTRs, 242 patients developed a skin cancer, with an incidence of 1,203.2 per 100,000 PYAR. In total, 230 patients developed NMSC (incidence: 1,143.5 per 100,000 PYAR) and 12 developed melanoma (incidence: 59.7 per 100,000 PYAR).

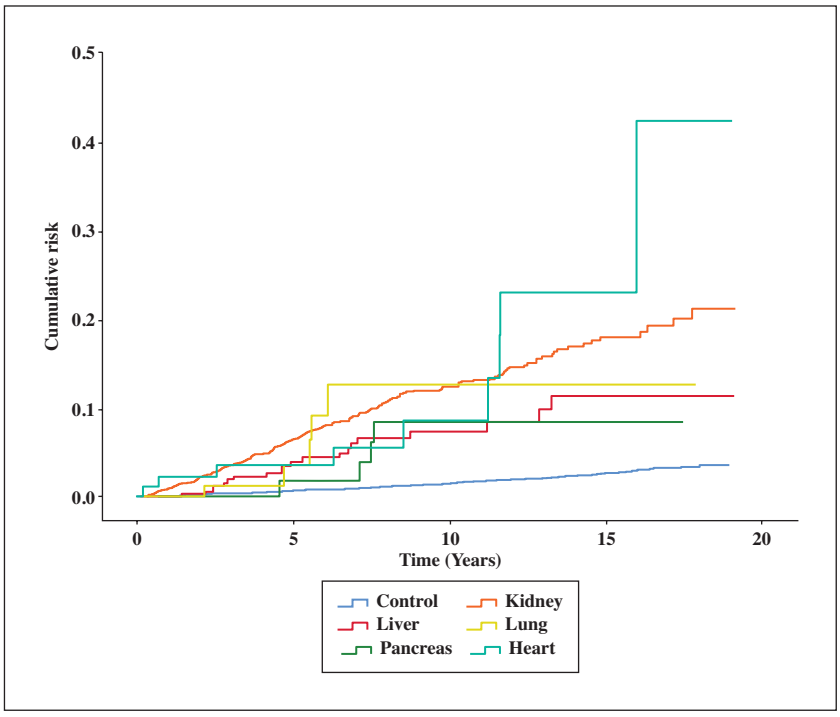

Figure 4. Cumulative risk of skin cancer per organ type.

Table 3. Multivariate analysis demonstrating incidence rate ratios.

Variable	*p* value	IRR (95% CIIRR)
Age at cohort entry**	0.00	1.08 (1.07-1.09)
Sex		
Female	*	
Male	0.01	1.47 (1.1.17-1.85)
WIMD Quintile		
1 (Lowest socioeconomic status)	*	
2	0.01	0.63 (0.45-0.89)
3	0.33	0.85(0.62-1.18)
4	0.38	0.86 (0.62-1.20)
5 (Highest socioeconomic status)	0.47	1.12 (0.83-1.51)
Organ transplanted		
Control	*	
Liver	0.00	4.34 (2.48-7.58)
Pancreas	0.00	10.67 (3.64-31.25)
Kidney	0.00	9.87 (7.26-13.43)
Lung	0.00	5.95 (2.20-16.13)
Heart	0.00	12.80 (5.63-29.09)
Steroid		
None	*	
Taken	0.72	1.07 (0.74-1.54)
Cyclosporin		
None	*	
Taken	0.27	1.27 (0.83-1.94)
Tacrolimus		
None	*	
Taken	0.37	0.83 (0.55-1.25)
Azathioprine		
None	*	
Taken	0.01	1.66 (1.16-2.36)
Mycophenolate		
None	*	
Taken	0.18	0.78 (0.54-1.12)
Sirolimus		
None	*	
Taken	0.73	1.10 (0.64-1.90)

**Reference Category. **Age used as a continuous variable*

Of the controls, 175 patients developed skin cancer, with an incidence of 153.1 per 100,000 PYAR. In total, 153 patients developed NMSC (incidence: 133.9 per 100,000 PYAR) and 22 patients developed melanoma (incidence: 19.2 per 100,000 PYAR). *Figure 3* displays the incidence of skin cancer per organ transplanted.

Cumulative risk of skin cancer

The cumulative risk of skin cancer per organ type is presented in *figure 4*.

Multivariate risk analysis

Multivariate risk analysis is presented in *table 3*.

Drug analysis

Multivariate analyses for drug regime, CNIs, comparison between CNIs and mTOR inhibitors, and antiproliferative agents are presented in *tables 4, 5, 6, 7*, respectively.

Discussion

To our knowledge, this is the first study reporting a comparison of skin cancer IRRs (for both melanoma and NMSC) between OTRs, according to different organ types, and a control population. Previous studies used kidney transplant recipients as the reference group [14] and reported higher incidence rates for both melanoma and NMSC in the transplant population compared to matched controls [23].

After adjusting for patient variables, considerable variation was observed between the IRRs for different organ types, with heart transplant recipients having the highest IRR compared to the control population. The lowest IRR was observed in liver transplant recipients. Heart transplant recipients require higher immunosuppressant dosages compared to recipients of other organ types [24, 25]; for liver transplants, there is a lower prevalence of humoral rejection, thus lower dosages of immunosuppressants are required [14, 26].

Male sex and increased patient age were demonstrated as factors associated with an increased incidence of skin cancer within the cohort, likely due to lifestyle factors (occupational exposure to UV) and the carcinogenic effect of androgens [27]. The risk associated with increased age is attributed to longer cumulative ultraviolet (UV) radiation exposure [16, 28-30].

In contrast to skin cancer in the general population, patients with a higher socioeconomic status did not have an increased rate of skin cancer development, which has often been attributed to lifestyle factors such as increased foreign travel [31, 32]. Our findings could be explained by the fact that OTRs have complex health needs and such lifestyle factors that contribute to increased skin cancer risk may not be relevant to such patients.

Our study shows that patients taking tacrolimus have a reduced risk of skin cancer development compared to OTRs taking cyclosporin, in line with previous studies [33, 34]. This reduced risk was also observed in patients that changed CNIs during the study. Cyclosporin has been demonstrated to inhibit calcineurin phosphatase activity more potently than tacrolimus [35], alongside its inhibitory effects on mitochondrial permeability, thus inhibiting apoptosis after oxidative (UVA-induced) cell damage [36].

No association was observed between sirolimus use and skin cancer risk, both based on individual drug multivariate analysis and in patients that switched from calcineurin inhibitors. Prior studies have shown a reduction in skin cancer risk in OTRs treated with sirolimus both as first-line therapy and after switching from a calcineurin inhibitor [37-47].

Increased activation of mTORC1 is observed in numerous human cancers due to gain-of-function mutations in oncogenes (*i.e.*, *PI3K*, *AKT*, or *Ras*) and/or loss-of-function mutations in tumour suppressors (*i.e.*, *PTEN*,

Table 4. Multivariate analysis of drug regimes.

Drug regime	N	*p* value	IRR	95% CI
1. Steroid + Azathioprine + Cyclosporin	41	*	*	*
2. Steroid + Mycophenolate + Tacrolimus	541	0.00	0.33	0.06-1.88
3. Steroid + Mycophenolate + Sirolimus	15	0.21	0.18	0.72-0.44

**Reference Category (After adjusting for patient variables and organ transplanted)*

Table 5. Multivariate analysis of CNIs.

Drug	N	*p* value	IRR	95% CI
Only cyclosporin	203	*	*	*
Only tacrolimus	1273	0.02	0.56	0.34-0.92
Switch from cyclosporin to tacrolimus	178	0.03	0.44	0.21-0.92

**Reference category (After adjusting for patient variables, organ transplanted, sirolimus and azathiprine use). Of those who switched from cyclosporin to tacrolimus, the median time duration of ciclosporin use was 2.6 years and the median duration of tacrolimus use was 5.2 years.*

Table 6. Multivariate analysis of switch from CNIs to mTOR inhibitors.

Drug	N	*p* value	IRR	95% CI
Only cyclosporin	203	*	*	*
Switched from cyclosporin to sirolimus	26	0.57	0.57	0.18-1.87
Only tacrolimus	1273	*	*	*
Switched from tacrolimus to sirolimus	75	0.40	1.37	0.65-2.90

**Reference Category (After adjusting for patient variables, organ transplanted, sirolimus and azathioprine use).*

Table 7. Multivariate analysis of antiproliferative agents.

Drug	N	*p* value	IRR	95% CI
Only azathioprine	352	*	*	*
Only mycophenolate	952	0	0.49	0.32-0.75
Switched from azathioprine to mycophenolate	309	0.34	0.77	0.46-1.31

**Reference Category (After adjusting for patient variables, organ transplanted, cyclosporin, sirolimus and tacrolimus use.) Of the patients who did not switch from azathioprine to mycophenolate, the median duration of azathioprine use was 3.35 years and the median duration of mycophenolate use was 5.8 years.*

LKB1, or *TSC1/2*); upstream regulators of mTORC1. These mutations provide cancer cells with a selective growth advantage in comparison to normal cells. In order to meet the high demands of proliferation, cancer cells often have fundamental alterations in nutrient uptake and energy metabolism, processes that are directly controlled by the mTORC1 pathway [48]. Inhibition of mTOR therefore has mechanistic potential to suppress the formation of skin cancers and the formation of other tumours in OTRs. Everolimus is already licenced for the treatment of several solid tumours [49].

The lack of statistical significance in our study could be explained by the relatively low number of patients in the study treated with sirolimus. A limitation of previous studies, however, is that they have been limited to a one-organ cohort and not controlled for other immunosuppressive medication. Further work is required to define their association with NMSC in greater detail.

Azathioprine was found to significantly increase the risk of skin cancer in this study. Patients taking mycophenolate instead of azathioprine, however, had a reduced risk of skin cancer development. Mycophenolate has been found to have significant antitumor activity with respect to a wide range of malignancies in murine studies *in vivo* [50, 51]. Azathioprine leads to 6-thioguanine (6TG) incorporation into the DNA of dividing cells [52]. 6TG DNA is a strong UVA chromophore which acts as a photosensitiser and acts synergistically with UVA to generate reactive oxygen species which lead to mutagenic DNA lesions [53].

Switching from azathioprine to mycophenolate during the study did not lead to a significant reduction in skin cancer risk compared to patients that remained on azathioprine. This would suggest that the carcinogenic effect of azathioprine continues after the drug has been stopped and therefore those patients who have any history of azathioprine use should be considered at higher risk of skin cancer development. This is supported by the detection of measurable DNA 6-TG in azathioprine patients as late as 28 months after the change to mycophenolate [54, 55].

Limitations of this study include the lack of data on ethnicity, UV light exposure and dosage and duration of immunosuppressant medication. The ethnicity issue is mitigated by population statistics showing that 95% of the population in Wales are Caucasian and therefore the significance of ethnicity on the results is minimal [56]. Unfortunately, ICD-10 coding only allows classification of tumours as melanoma or NMSC, and current available datasets do not hold details on the histological subtype or differentiation between basal cell carcinomas and squamous cell carcinomas. We are working with data analysts and coders to allow this in future analyses.

Recommendations for health care professionals

This study demonstrates that the incidence of skin cancer in the transplant population is considerably higher than that in the general population. Clinicians should be aware that contemporary immunosuppressant medications (mycophenolate and tacrolimus) have a lower skin cancer risk profile compared to their older counterparts (azathioprine and cyclosporin). Our study also demonstrates that azathioprine continues to increase a patient's risk after it has been discontinued and therefore clinicians should take a thorough drug history to establish previous immunosuppression regimes. The risk profile of mTOR-based medications is not fully understood and further research into this area is warranted. At present, skin cancer care in OTRs is reactive rather than proactive. Multiple models of care, including improved patient education and specialist skin cancer clinics, have been described in the literature with promising results, strongly supporting recommendations from SCOPE (Skin Cancer in Organ Transplant Patients, Europe) and ITSCC (International Transplant Skin Cancer Collaborative) [57, 58]. Both organisations recommend that all OTRs should be reviewed in a multi-disciplinary clinic to enhance photoprotection but to ensure early detection of skin cancers. In our previous published study, we have found that this is not adhered to in all areas and that skin cancer care in OTRs is reactive rather than proactive [13]. This work supports the need for long-term skin surveillance within this high-risk population and highlights the patients most at risk. Closer collaboration between skin cancer specialists and transplant teams would be beneficial for patient education, early identification and prompt treatment of skin cancer.

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This study makes use of anonymised data held in the Secure Anonymised Information Linkage (SAIL) Databank. We would like to acknowledge all the data providers who make anonymised data available for research. Conflicts of interest: none.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1684/ejd.2021.4108.
Table S1 : The RECORD statement – checklist of items, extended from the STROBE statement, that should be reported in observational studies using routinely collected health data.
Table S2 : OPCS4 procedure codes used to indicate a major Organ Transplant.
Table S3 : READ codes used to identify immunosuppressant drugs.
Table S4 : The following ICD 10 codes were used to identify skin cancer.C43 Malignant melanoma of skin and sub codes.
Table S5 : Demographics of cases and controls.

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