VIA MEDICA

REVIEW ARTICLE

Wojciech M. Wysocki[1–3], **Aleksandra Kulbat**[1, 2, 4]

[1]Chair of Surgery, Faculty of Medicine and Health Sciences, Andrzej Frycz Modrzewski Krakow University, Poland
[2]Department of Oncological Surgery, 5th Military Clinical Hospital, Kraków, Poland
[3]Editorial Office, Maria Skłodowska-Curie Memorial National Research Institute of Oncology, Warsaw, Poland
[4]Department of Breast Cancer and Reconstructive Surgery, Maria Skłodowska-Curie Memorial National Research Institute of Oncology, Warsaw, Poland

Where there's smoke, there's fire — a brief report on skin malignancy incidence in renal, heart, and liver transplant recipients in Poland

Address for correspondence:
Aleksandra Kulbat, MD
Chair of Surgery, Faculty of Medicine and Health Sciences, Andrzej Frycz Modrzewski Krakow University
ul. Gustawa Herlinga-Grudzińskiego 1, 30–705 Kraków, Poland
e-mail: alexandra.kulbat@gmail.com

Oncology in Clinical Practice
DOI: 10.5603/ocp.103839

ISSN 2450–1654
e-ISSN 2450–6478

ABSTRACT

Introduction. The number of solid organ transplants is rising, increasing the population of long-term survivors. Immunosuppressive drugs, particularly calcineurin inhibitors, are linked to higher skin malignancy incidence, but large-scale studies on melanoma and non-melanoma skin cancer (NMSC) in Polish transplant recipients are lacking.

Materials and methods. This study combines findings from a systematic review and meta-analysis on the risks of NMSC and melanoma in renal transplant patients using calcineurin inhibitors. It also presents a large dataset from Poland's National Health Fund on skin malignancies incidence in kidney, heart, and liver transplant recipients (2010–2022).

Results. The authors of this article analyzed data from over 17,000 Polish transplant recipients and compared skin malignancy incidence versus the general population. Renal transplant patients had higher NMSC risk: 1-year (0.09% *vs.* 0.04%, $p < 0.001$), 5-year (1.21% *vs.* 0.18%, $p < 0.001$), and 10-year (4.18% *vs.* 0.36%, $p < 0.001$). Liver transplant recipients showed increased NMSC risk at 1-year (0.09% *vs.* 0.04%, $p < 0.001$), 5-year (0.83% *vs.* 0.18%, $p < 0.001$), and 10-year (2.65% *vs.* 0.36%, $p < 0.001$). Heart recipients had higher NMSC risk at 5 years (0.8871% *vs.* 0.1774%, $p < 0.001$) and 10 years (4.0609% *vs.* 0.3597%, $p < 0.001$). Melanoma risk in renal recipients was increased: 1-year (0.02% *vs.* 0.01%, $p < 0.001$), 5-year (0.17% *vs.* 0.05%, $p < 0.001$), 10-year (0.36% *vs.* 0.1%, $p < 0.001$). Liver recipients had higher melanoma risk at 1 year (0.03% *vs.* 0.01%, $p < 0.001$), 5 years (0.2% *vs.* 0.05%, $p < 0.001$) and 10 years (0.2% *vs.* 0.1%, $p < 0.001$).

Conclusions. The authors of this article nationwide dataset showed a significant association between heart, kidney, and liver transplantation followed by immunosuppression and an increased incidence of melanoma and NMSC. The melanoma risk in renal, liver, and heart transplant recipients in Poland was, on average, twice as high compared to the general population at 1 year, four and half times higher after 5 years, and almost nine times higher after 10 years. Similarly, the NMSC risk in this population was two and a half times higher after 1 year, seven and a half times higher after 5 years, and remained twenty two times higher after 10 years.

Keywords: nonmelanoma skin cancer, melanoma, transplant recipients, organ transplantation, calcineurin inhibitors, kidney transplantation, liver transplantation, heart transplantation, skin cancer risk

Oncol Clin Pract

Received: 01.12.2024 Accepted: 03.02.2025 Early publication: 20.02.2025

Introduction

There is a constantly growing number of solid organ transplants in Poland and worldwide [1, 2]. Not only is the absolute number of successful transplants rising, but the indications for transplantation are also expanding as new scientific data emerge [3, 4]. Therefore, the total population of long-term transplant survivors is increasing both locally (in Poland) and globally [1, 2, 4, 5].

Solid organ transplant recipients are subjected to lifelong immunosuppressive treatment to preserve proper graft function. There are numerous consequences of long-term use of immunosuppressive drugs, but from an oncological perspective, their association with the incidence of skin malignancies is of particular concern [6, 7].

The results of previously published studies indicate that transplant recipients face a 1,5- to 8-fold increased risk of skin melanoma compared to the general population. The degree of this increase varies significantly depending on the population studied, including its geographical location [7–9]. Melanoma after organ transplantation is associated with significant mortality [10]. Several studies have examined the risk of skin melanoma post-transplantation, demonstrating a wide and diverse range of increased incidence [8–10].

Scandinavian data report a 20- to 100-fold increase in the risk of developing non-melanoma skin cancer (NMSC) after transplantation [8]. Dutch data show that the risk of developing NMSC is 10% after 10 years and can rise to 40% after 20 years from organ transplantation [11]. Non-melanoma skin cancers, mainly squamous cell carcinoma (SCC) and basal cell carcinoma (BCC), are the most common tumors developing after organ transplantation, accounting for over 90% of all skin tumors in transplant recipients [12].

Effect on immunosuppression type on skin malignancies

Calcineurin inhibitors [CNI; mainly cyclosporine A (CsA) or tacrolimus (Tac)] are immunosuppressive drugs widely used in the post-transplantation period to prevent the rejection of the transplanted organ [13, 14]. In some studies, the use of CNI has been associated with an elevated risk of developing various skin malignancies in renal transplant recipients due to continuous immunosuppression; however, the underlying pathomechanism has been discussed in the literature without specific conclusions so far [15].

The authors of this article have recently published an extensive meta-analysis on the incidence of melanoma and NMSC in kidney transplant recipients receiving immunosuppression with a CNI, such as CsA or Tac, and compared this group to patients receiving alternative immunosuppressants. The authors of this article study included 7 articles and encompassed a total of 309 551 cases. The authors of this article analyzed overall skin cancer risk, melanoma risk and NMSC risk separately. The authors of this article demonstrated that there is a correlation between CNI treatment in renal transplant recipients and an increased overall skin cancer risk [odds ratio (OR) = 1.28; 95% confidence interval (CI) 0.10–16.28; $p < 0.01$], melanoma risk (OR = 1.09; 95% CI 0.25–4.74; $p < 0.01$), and NMSC risk (OR = 1.16; 95% CI 0.41–3.26; $p < 0.01$), compared to patients taking immunosuppression without CNI.

Since CNIs remain the most common type of immunosuppression in transplant recipients, the practical conclusion from the authors of this article study is that transplantologists should pay special attention to cutaneous lesions in their patients who survive long-term after transplantation [16].

Skin malignancies incidence in total > 17,000 Polish transplant recipients

There have been no large-scale analysis on the change in skin malignancies, such as melanoma and NMSC, among Polish solid organ transplant recipients. That is why the authors of this article designed several studies focusing on this specific population in the context of skin malignancies.

The authors of this article based them epidemiological studies on Poland's National Health Fund (public health insurance governmental institution) databases. Initially, the authors of this article obtained data on the occurrence of melanoma and NMSC in patients who underwent kidney, heart, and liver transplants from 2010 to 2022 (specific codes used for transplantation reimbursements were utilized to identify relevant patients). To detect cutaneous melanoma and NMSC occurrence in the post-transplantation period, the authors of this article searched for International Classification of Diseases, 10th Revision, Clinical Modification [ICD-10-CM] codes (C43 and C44, respectively) in the previously identified database of transplant recipients over the years following transplantation. Additionally, the authors of this article compared the obtained results with data on the incidence of melanoma, SCC and BCC in the general population of Poland from 2010 to 2022 provided by the National Cancer Registry database [17].

In total, data on the occurrence of NMSC were retrieved for 17,207 patients who underwent liver, heart, or kidney transplants between 2010 and 2022. The authors of this article found that renal transplant recipients demonstrated a significantly elevated risk of NMSC

Table 1. Cumulative incidence rate of non-melanoma skin cancer (NMSC) (C44) over time in patients with heart transplantation (Tx) liver Tx, heart Tx compared to the general population

Follow-up	Cumulative incidence rate (%)		p value	Cumulative incidence rate (%)		p value	Cumulative incidence rate (%)		p value
	Renal Tx	Population		Liver Tx	Population		Heart Tx	Population	
1 yr.	10 (0.0857%)	13,516 (0.0355%)	< 0.001	3 (0.0931%)	13,516 (0.0355%)	< 0.001	1 (0.0909%)	13,516 (0.0355%)	< 0.001
5 yr.	112 (1.2145 %)	67,490 (0.1774%)	< 0.001	19 (0,8311%)	67,490 (0.1774%)	< 0.001	6 (0.8871%)	67,490 (0.1774%)	< 0.001
10 yr.	250 (4.1835%)	136,838 (0.3597%)	< 0.001	35 (2.6462%)	136,838 (0.3597%)	< 0.001	13 (4.0609%)	136,838 (0.3597%)	< 0.001

Table 2. Cumulative incidence rate of melanoma (C43) over time in patients with heart transplantation (Tx), liver Tx, heart Tx compared to the general population

Follow-up	Cumulative incidence rate (%)		p value	Cumulative incidence rate (%)		p value	Cumulative incidence rate (%)		p value
	Renal Tx	Population		Liver Tx	Population		Heart Tx	Population	
1 yr.	2 (0.0171%)	3,168 (0.0083%)	< 0.001	1 (0.0310%)	3,168 (0.0083%)	< 0.001	0 (0%)	3,168 (0.0083%)	0.002
5 yr.	16 (0.1667%)	17,940 (0.0472%)	< 0.001	5 (0.2043%)	17,940 (0.0472%)	< 0.001	1 (0.1623%)	17,940 (0.0472%)	< 0.001
10 yr.	26 (0.3578%)	37,323 (0.0981%)	< 0.001	5 (0.2043%)	37,323 (0.0981%)	< 0.001	1 (0.1623%)	37,323 (0.0981%)	0.007

compared to the general population (1-year cumulative incidence of NMSC was 0.09% in transplant recipients *vs*. 0.04% in the general population, $p < 0.001$; 5-year cumulative incidence 1.2% *vs.* 0.18%, $p < 0.001$, respectively; the 10-year cumulative incidence 4.2% *vs.* 0.36%, $p < 0.001$, respectively) (Tab. 1).

Liver transplant recipients also exhibited a significantly elevated risk for the development of NMSC, which persisted and increased over time since organ transplantation (1-year cumulative incidence of NMSC was 0.09% in transplant recipients *vs*. 0.04% in general population, $p < 0.001$; 5-year cumulative incidence 0.83% *vs.* 0.18%, $p < 0.001$, respectively; the 10-year cumulative incidence 2.6% *vs.* 0.36%, $p < 0.001$, respectively) (Tab. 1).

The authors of this article also observed that heart transplant recipients showed a significantly higher cumulative incidence of NMSC at 1- (0.09% *vs.* 0.04% , $p < 0.001$, respectively), 5- (0.89% *vs.* 0.18% , $p < 0.001$, respectively) and 10- years (4.06% *vs.* 0.36, $p < 0.001$, respectively) post-transplantation. [18] (Tab. 1).

The other study examined cutaneous melanoma in renal (12,205 cases), liver (3,584 cases), and heart (1,418 cases) transplant recipients over a period of thirteen years. The authors of this article showed that melanoma incidence slightly increased in renal recipients (1-year cumulative incidence 0.02% *vs*. 0.01%, $p < 0.001$; 5-year cumulative incidence 0.17% *vs.* 0.05% $p < 0.001$; the 10-year cumulative incidence 0.36% *vs.* 0.1, $p < 0.001$) compared to the general population. A similar comparison performed in liver transplant recipients showed a significant difference at 1 year after transplantation (cumulative incidence 0.03% *vs.* 0.01%, $p < 0.001$), at 5 and 10 years the (5-year cumulative incidence 0.21% *vs.* 0.05%, $p < 0.001$; the 10-year cumulative incidence 0.21% *vs.* 0.1%, $p < 0.001$). Surprisingly, in heart transplant recipients, a paradoxical decrease in the occurrence of melanoma was observed compared to the general population (1-year cumulative incidence 0% *vs.* 0.01%, $p = 0.002$; 5-year cumulative incidence 0.16% *vs.* 0.05%, $p < 0.001$; the 10-year cumulative incidence 0.16% *vs.* 0.1, $p < 0.007$). However, this might be attributed to the relatively small sample size in the early years (2010–2014). The data presented in this article are put forward according to a slightly modified statistical methodology to facilitate comparison with data on NMSC. As a result, they differ slightly from the data in the source article [19] (Tab. 2).

Limitations of the authors of this article studies

What the authors of this article consider a limitation of the authors of this article research so far is exclusion of some other transplanted organs from the authors of this article dataset. The authors of this article attempted to include lung and other solid organ recipients in the analysis, however, these organs are transplanted much less frequently, and due to the complexity of these procedures, the success rate is significantly lower. This, in turn, results in a smaller number of long-term survivors taking immunosuppression and consequently, a lower number of registered melanoma and NMSC occurrence in these subgroups. Therefore, the authors of this article decided to exclude solid organ transplants other than heart, kidney, and liver from further analysis.

Another limitation the authors of this article encountered is the lack of sufficient information regarding the immunosuppressive drugs used by the recipients. This is due to the small number of patients taking medications other than the most commonly used immunosuppressive treatment regimen for solid organ transplant recipients, i.e.: tacrolimus (TAC)/CsA + mycophenolic acid (MPA) + glucocorticosteroids (GS). A detailed analysis of the specific immunosuppressive treatment regimens and their impact on the development of skin malignancies is the subject of the authors of this article subsequent research. The aforementioned publications are intended solely to outline the clinical relevance and significance of the issue being addressed.

Moreover, follow-ups after 5 and 10 years included only a portion of the patients, as the authors of this article still have incomplete data in this regard. However, by taking the total number of kidney, heart, and liver transplants performed between 2010 and 2022 as a reference point, the authors of this article were able to obtain a more representative cohort. This increases the credibility of the results and allows for a better understanding of the impact of transplantation on the occurrence of skin cancers in this specific population.

Strengths of the authors of this article studies

Despite the aforementioned limitations, the authors of this article series of studies outlined in this review represent the first attempt to analyze a Polish nation-wide large dataset on melanoma and NMSC incidence in selected solid organ transplant recipients. A total of 1910 organ transplants, including 1055 kidney transplants, 550 liver transplants, and 178 heart transplants, were carried out in Poland in 2023, according to the National Health Fund, significantly surpassing the 1608 transplants performed in 2012 [1]. The authors of this article results provide detailed information on real-world skin malignancy incidence in the growing population of Polish kidney, heart, and liver transplant recipients living with lifelong immunosuppression.

Additionally, to enhance the reliability of the initial dataset, the authors of this article performed cross-verification of National Health Fund data with the Poltransplant dataset, with great support from Division of Databases and Analytical Tools, Department of Analysis, Quality Monitoring, and Service Optimization). The authors of this article compared the number of patients extracted from the National Health Fund databases with the data provided by Poltransplant to create the most reliable and consistent patient population, which the authors of this article then subjected to further analysis. The strength of the authors of this article reports lies in the thorough examination of accessible data, strict inclusion criteria, and their integration to achieve a clinically meaningful results.

The epidemiological results presented in the authors of this article studies could be valuable for Polish health-policymakers and health professionals. These data may also be useful for other countries in the authors of this article region of Europe that share a similar geographical latitude, as sun exposure combined with long-term immunosuppression are the two leading factors for melanoma and NMSC in post-transplantation patients.

Conclusions

The authors of this series of studies [6, 16, 18, 19] confirm, using a nationwide real-world dataset, a statistically significant association between heart, kidney, and liver transplantation followed by immunosuppression and an increased incidence of melanoma and non-melancytic skin cancer in the post-transplant period. The melanoma risk in renal, liver, and heart transplant recipients in Poland was, on average, twice as high compared to the general population at 1 year, four and a half times higher after 5 years, and almost nine times higher after 10 years. Similarly, the NMSC risk in this population was two and a half times higher after 1 year, seven and a half times higher after 5 years, and remained twenty two times higher after 10 years.

The authors of this article findings, apart from their epidemiological value, highlight the clinical importance of regular and long-lasting skin follow-ups in solid organ transplant recipients. This is reflected in recently published Polish surveillance guidelines for selected skin cancers [20]. Implementation of regular dermatological monitoring programs could contribute to improved overall treatment outcomes and reduced mortality from skin cancers in the post-transplant population.

Article Information and Declarations

Author contributions

W.W.: conceived and designed the study, performed the study, analyzed the data, drafted the manuscript, wrote the final version of the manuscript, reviewed and revised the manuscript for important intellectual content;A.K.: performed the study, analyzed the data, prepared the figures, drafted the manuscript, wrote the final version of the manuscript.
All authors read and approved the final version of the manuscript.

Funding

The preparation of this paper was partially supported by grants WSUB/2023/07/00009 and WSUB/2024/02/00002 at Andrzej Frycz Modrzewski Krakow University.

Acknowledgments

The authors of this article thank the National Health Found for providing data and collaborating in the preparation of this article. The authors of this article acknowledge their commitment to advancing scientific endeavors and their dedication to promoting the accessibility of healthcare data for research purposes.

Conflicts of interest

The authors declare no conflict of interest.

Supplementary material

None.

References

1. Poltransplant Statystyka 2023. http://www.poltransplant.org.pl/statystyka_2023.html#gsc.tab=0 (14.07.2024).
2. INTERNATIONAL REPORT ON Organ Donation and Transplantation Activities 2022. https://www.transplant-observatory.org/wp-content/uploads/2023/11/2022-data-global-report_VF_2.pdf (14.07.2024).
3. Wu MY, Ali Khawaja RD, Vargas D. Heart Transplantation: Indications, Surgical Techniques, and Complications. Radiol Clin North Am. 2023; 61(5): 847–859, doi: 10.1016/j.rcl.2023.04.011, indexed in Pubmed: 37495292.
4. Fridell JA, Stratta RJ. Modern indications for referral for kidney and pancreas transplantation. Curr Opin Nephrol Hypertens. 2023; 32(1): 4–12, doi: 10.1097/MNH.0000000000000846, indexed in Pubmed: 36444661.
5. Irish GL, Campbell S, Kanellis J, et al. Temporal validation of the Australian estimated post-transplant survival score. Nephrology (Carlton). 2023; 28(5): 292–298, doi: 10.1111/nep.14158, indexed in Pubmed: 36941195.
6. Kulbat A, Wysocki W. Multiple non-melanoma skin cancers during 43-years long therapy with azathioprine in renal transplant recipient. Nowotwory. Journal of Oncology. 2024, doi: 10.5603/njo.100154.
7. Lizakowski S, Rutkowski P. Nowotwory u chorych o rzeszczeieniu nerki. In: Rutkowski P. ed. Leczenie nerkozastępcze. Czelej, Lublin 2007: 409–418.
8. Birkeland SA, Storm HH, Lamm LU, et al. Cancer risk after renal transplantation in the Nordic countries, 1964-1986. Int J Cancer. 1995; 60(2): 183–189, doi: 10.1002/ijc.2910600209, indexed in Pubmed: 7829213.
9. Jensen P, Hansen S, Møller B, et al. Skin cancer in kidney and heart transplant recipients and different long-term immunosuppressive therapy regimens. J Am Acad Dermatol. 1999; 40(2 Pt 1): 177–186, doi: 10.1016/s0190-9622(99)70185-4, indexed in Pubmed: 10025742.
10. Erdei E, Torres S. A new understanding in the epidemiology of melanoma. Expert Rev Anticancer Ther. 2014; 10(11): 1811–1823, doi: 10.1586/era.10.170, indexed in Pubmed: 21080806.
11. Hartevelt MM, Bavinck JN, Kootte AM, et al. Incidence of skin cancer after renal transplantation in The Netherlands. Transplantation. 1990; 49(3): 506–509, doi: 10.1097/00007890-199003000-00006, indexed in Pubmed: 2316011.
12. Acuna SA. Etiology of increased cancer incidence after solid organ transplantation. Transplant Rev (Orlando). 2018; 32(4): 218–224, doi: 10.1016/j.trre.2018.07.001, indexed in Pubmed: 30017342.
13. Parlakpinar H, Gunata M. Transplantation and immunosuppression: a review of novel transplant-related immunosuppressant drugs. Immunopharmacol Immunotoxicol. 2021; 43(6): 651–665, doi: 10.1080/08923973.2021.1966033, indexed in Pubmed: 34415233.
14. Tönshoff B. Immunosuppressants in Organ Transplantation. Pediatric Pharmacotherapy. 2019: 441–469, doi: 10.1007/164_2019_331.
15. Parlakpinar H, Gunata M. Transplantation and immunosuppression: a review of novel transplant-related immunosuppressant drugs. Immunopharmacol Immunotoxicol. 2021; 43(6): 651–665, doi: 10.1080/08923973.2021.1966033, indexed in Pubmed: 34415233.
16. Kulbat A, Richter K, Stefura T, et al. Systematic Review of Calcineurin Inhibitors and Incidence of Skin Malignancies after Kidney Transplantation in Adult Patients: A Study of 309,551 Cases. Curr Oncol. 2023; 30(6): 5727–5737, doi: 10.3390/curroncol30060430, indexed in Pubmed: 37366913.
17. Krajowy Rejestr Nowotworów - Raporty. https://onkologia.org.pl/pl/raporty (21.11.2024).
18. Wysocki WM, Kulbat A, Richter K, et al. Squamous and basal skin cancers in 17,207 solid organ transplant recipients: Real-world data from national health insurance database in Poland. Adv Clin Exp Med. 2025 [Epub ahead of print], doi: 10.17219/acem/199653, indexed in Pubmed: 39912318.
19. Kulbat A, Richter K, Krzysztofik M, et al. Melanoma incidence in 17,252 organ transplant recipients in Poland in 2010–2022. Nowotwory. Journal of Oncology. 2024, doi: 10.5603/njo.99186.
20. Wysocki W, Kulbat A, Krzysztofik M, et al. Post-treatment Surveillance Principles for Selected Skin Cancers – recommendations of the Surveillance Standardization Section of the Polish Oncology Society. Nowotwory. Journal of Oncology. 2024; 74(3): 197–202, doi: 10.5603/njo.99894.