Federacja Naukowa
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DYSCYPLINA NAUKI MEDYCZNE

lek. Aleksandra Kulbat

Czerniak skóry i wybrane niemelanocytarne nowotwory skóry u pacjentów po przeszczepieniu wybranych narządów litych

Melanoma skin cancer and selected non-melanoma skin cancers in patients after transplantation of selected solid organs

Rozprawa doktorska przygotowana pod kierunkiem
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SPIS TREŚCI

1. Wykaz publikacji wchodzących w skład rozprawy doktorskiej

1. **Kulbat A.**, Richter K., Stefura T., Kołodziej-Rzepa M., Kisielewski M., Wojewoda T., Wysocki W.M.: 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.

   punkty MNiSW: 70

   impact factor (2023): 2,8

2. **Kulbat A.**, Richter K., Krzysztofik M., Batko K., Karwańska A., Kołodziej-Rzepa M., Wojewoda T., Wysocki W.M.: Melanoma incidence in 17,252 organ transplant recipients in Poland in 2010–2022. *Nowotwory J. Oncol*., 2024; 74: 173–179 doi:10.5603/njo.99186.

   punkty MNiSW: 100

3. Wysocki W.M., **Kulbat A.,** Richter K., Krzysztofik M., Kołodziej-Rzepa M., Wojewoda T.: 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. doi:10.17219/acem/199653.

   punkty MNiSW: 70

   impact factor (2025): 1,9

4. **Kulbat A.,** Wysocki W.M.: Multiple non-melanoma skin cancers during 43-years long therapy with azathioprine in renal transplant recipient. *Nowotwory J. Oncol.,* 2024, 74. doi:10.5603/njo.100154.

   punkty MNiSW: 100

   Łącznie:

   punkty MNiSW: 340

   ***impact factor*: 4,7**

2. Wstęp

Zgodnie z danymi publikowanymi w corocznych Biuletynach Informacyjnych Poltransplantu liczba biorców przeszczepionych narządów litych w Polsce w ostatnich latach stale wzrasta. W 2024 r. osiągnęła 2197 biorców, z których prawie 90% stanowili biorcy nerki, wątroby lub serca [1]. Globalnie, jak podaje Światowa Organizacja Zdrowia (ang. *World Health Organization* – WHO), populacja biorców przeszczepu corocznie zwiększa się o kilkaset tysięcy osób [2].

Przeszczepienie narządu litego często jest jedyną skuteczną formą leczenia schyłkowej niewydolności narządu i daje możliwość wydłużenia i poprawy jakości życia pacjentów. Niesie jednak za sobą nie tylko korzyści, ale także ograniczenia i obowiązki, które mają na celu przedłużenie żywotności przeszczepionego narządu. Koniecznością dla pacjentów po przeszczepieniu nerki, wątroby i serca jest terapia immunosupresyjna, która zapobiega odrzuceniu przeszczepionego narządu przez organizm biorcy. Ta forma terapii, choć skuteczna w kontekście przedłużenia żywotności przeszczepu, obniża także zdolność organizmu do wykrywania i eliminowania patogenów, czy komórek nowotworowych. Zwiększa to ryzyko nowotworzenia w tej grupie pacjentów, w porównaniu z ryzykiem w populacji ogólnej [3, 4].

Nowotworami złośliwymi najczęściej występującymi u pacjentów po przeszczepieniu narządów litych są niemelanocytarne nowotwory skóry (ang. *non-melanoma skin cancer* –NMSC) [5, 6]. U biorców tych narządów ryzyko zachorowania na nowotwory skóry jest od 2 do 250 razy większe w porównaniu z populacją ogólną, przy czym w największym stopniu jest ono zwiększone w Australii, gdzie jest 250 razy większe niż w populacji ogólnej [7]. Badania skandynawskie wskazują na 20–100-krotne zwiększenie ryzyka rozwoju NMSC u biorców narządów litych w porównaniu z ryzykiem populacyjnym [8, 9]. Choć rak

płaskonabłonkowy (ang. *squamous cell carcinoma* – SCC) i rak podstawnokomórkowy (ang. *basal cell carcinoma* – BCC) rzadko prowadzą do zgonu, to mogą powodować destrukcję tkanek, ich deformację i zaburzenia czynnościowe [10]. Badania pokazują, że u chorych na NMSC również ryzyko powstania przerzutów w węzłach chłonnych i narządach wewnętrznych jest większe wśród biorców przeszczepów [11]. To dodatkowo podkreśla wagę wczesnego wykrywania i radykalnego leczenia tych nowotworów u osób z obniżoną (także jatrogennie) odpornością.

Czerniak skóry, choć jego przypadki stanowią zaledwie 1-3% wszystkich zachorowań na nowotwory skóry, cechuje się agresywnym przebiegiem i odpowiada za większą część związanych z nimi zgonów. Dotychczasowe badania, przeprowadzone w różnych krajach świata, jednoznacznie wykazały, że ryzyko zachorowania na czerniaka skóry u biorców przeszczepów narządów litych jest od 1,5 do nawet 8 razy większe w porównaniu z populacją ogólną [3–4, 12]. Dane europejskie również wskazują na zróżnicowanie częstości występowania czerniaka skóry u biorców przeszczepów, pomimo podobieństwa dodatkowych czynników ryzyka w większości krajów europejskich, wynikającego ze zbliżonego położenia geograficznego.

Mimo ciągłego postępu w diagnostyce i leczeniu, nowotwory skóry wciąż stanowią istotny, a często także marginalizowany problem w grupie biorców przeszczepów narządów litych, u których ryzyko zachorowalności jest szczególnie wysokie. Wysoka częstość występowania nowotworów skóry w tej grupie pacjentów ma kilka przyczyn. Po pierwsze, wynika ze stosowania leków immunosupresyjnych, które upośledzają mechanizmy odporności na dodatkowe czynniki ryzyka (takie jak promieniowanie UV, czy infekcje wirusem brodawczaka ludzkiego [ang. *human papilloma virus* – HPV]) [13–16]. Po drugie, jest związana ze zmianami w funkcjonowaniu układu immunologicznego towarzyszącymi chorobie

podstawowej [17, 18]. Dodatkowo, występujące u pacjentów z tej grupy nowotwory skóry częściej cechują się nietypowym obrazem klinicznym oraz zwiększonym zaawansowaniem w chwili rozpoznania i gorszym ogólnym rokowaniem [19]. Wymaga to niewątpliwie wzmożonego nadzoru nad chorymi i szczególnych zasad prowadzenia opieki.

Wczesne wykrycie nowotworu skóry u chorego po przeszczepieniu narządu litego i szybkie wdrożenie leczenia znacznie poprawiają rokowanie i zwiększają odsetki przeżywalności. Wprowadzenie odpowiednich strategii monitorowania biorców narządów litych (w postaci regularnego badania dermatoskopowego) oraz edukacja na temat ochrony przeciwsłonecznej są istotnymi elementami opieki nad tą grupą pacjentów [19–21]. Jednakże fundamentalnym, niezbędnym krokiem w drodze do opracowania i wdrożenia odpowiednich zasad jest poznanie rzeczywistego ryzyka zachorowania w danej populacji (w tym przypadku – w naszym kraju). Jak wcześniej wskazaliśmy, nie analizowano dotąd pod tym kątem ogólnopolskich zasobów danych Narodowego Funduszu Zdrowia, Poltransplantu i Krajowego Rejestru Nowotworów.

3. Uzasadnienie i cele rozprawy doktorskiej

Według najnowszej wiedzy w Polsce nie przeprowadzono do tej pory dużej, wieloośrodkowej analizy epidemiologicznej dotyczącej częstości występowania czerniaka skóry (ang. *cutaneous melanoma* – CM) i niemelanocytarnych nowotworów skóry (ang. *non-melanoma skin cancer* – NMSC) u biorców narządów litych. Dostępne informacje mają jedynie charakter lokalny, są ograniczone do pojedynczych ośrodków i nie pozwalają na całościowe zobrazowanie istoty problemu w naszym kraju [22]). Uznaliśmy zatem, że istnieje pilna potrzeba analitycznego opracowania danych o charakterze populacyjnym, swoistych dla naszego kraju, które pozwolą określić rzeczywiste ryzyko wystąpienia CM i NMSC w grupie pacjentów po przeszczepieniu narządu litego. Dane te mogą posłużyć do sformułowania ogólnopolskich wytycznych w zakresie monitorowania i wczesnego wykrywania nowotworów skóry u biorców przeszczepów.

1. **Celem głównym** niniejszej rozprawy doktorskiej była ocena częstości występowania czerniaka skóry i niemelanocytarnych nowotworów skóry u biorców wybranych narządów litych, takich jak nerka, wątroba i serce, którzy w okresie po przeszczepieniu zostali poddani terapii immunosupresyjnej w Polsce.

2. **Cele szczegółowe**:

   2.1. Przeprowadzenie przeglądu systematycznego i metaanalizy danych z dostępnego piśmiennictwa naukowego, dotyczących częstości występowania MSC (ang. *melanoma skin cancer* – MSC) i NMSC u biorców nerki, którzy byli leczeni inhibitorami kalcyneuryny (ang. *calcineurin inhibitors* – CNI) oraz porównanie z częstością występowania MSC i NMSC u pacjentów stosujących wyłącznie inne leki immunosupresyjne.

2.2. Pozyskanie oraz analiza porównawcza danych z Narodowego Funduszu Zdrowia (NFZ) i Krajowego Rejestru Nowotworów (KRN) z następową oceną ryzyka występowania MSC u biorców nerki, wątroby lub serca w Polsce.

2.3. Pozyskanie oraz analiza porównawcza danych z NFZ i KRN z następową oceną częstości występowania NMSC u biorców nerki, wątroby lub serca w Polsce.

2.4. Sformułowanie wniosków pozwalających na określenie zasad kontroli onkologicznej pacjentów po przeszczepieniu narządów litych w kontekście wczesnego wykrywania nowotworów skóry.

4. Pełne teksty publikacji wchodzących w skład rozprawy doktorskiej

Current Oncology

MDPI

Systematic Review

Systematic Review of Calcineurin Inhibitors and Incidence of Skin Malignancies after Kidney Transplantation in Adult Patients: A Study of 309,551 Cases

Aleksandra Kulbat [1,2,3], Karolina Richter [4], Tomasz Stefura [2,3], Marta Kołodziej-Rzepa [2,4], Michał Kisielewski [2,4], Tomasz Wojewoda [2,4] and Wojciech M. Wysocki [1,2,4,*]

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Abstract: The purpose of this systematic review and meta-analysis was to compare the risk of non-melanoma skin cancer (NMSC) and melanoma development in renal transplant recipients who receive calcineurin inhibitors to that of patients treated with other immunosuppressive agents, and investigate the possible association between the type of maintenance immunosuppression and the incidence of NSMC and melanoma in this group of patients. The authors searched databases such as PubMed, Scopus, and Web of Science for articles that would help establish the influence of calcineurin inhibitors on skin cancer development. The inclusion criteria for the study consisted of randomized clinical trials, cohort studies, and case-control studies that compared patients who received kidney transplants and were treated with a calcineurin inhibitor (CNI), such as cyclosporine A (CsA) or tacrolimus (Tac), to those who received alternative immunosuppressants and did not receive a CNI. Seven articles were analyzed overall. The results revealed a correlation between CNI treatment in renal transplant recipients and increased total skin cancer risk (OR 1.28; 95% 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; $p < 0.01$). In conclusion, the calcineurin inhibitors used after kidney transplantation are associated with a higher risk of skin cancer—both non-melanoma and melanoma—when compared with other immunosuppressive therapies. This finding suggests that careful monitoring for skin lesions in post-transplant patients must be conducted. However, the decision on the kind of immunotherapy used should always be considered on an individual basis for each renal transplant recipient.

Keywords: calcineurin inhibitors; cyclosporine; tacrolimus; skin cancer; melanoma skin cancer; non-melanoma skin cancer; renal transplant recipients; renal transplantation; meta-analysis

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1. Introduction

According to the World Health Organization (WHO), approximately 300,000 kidney transplants are performed each year worldwide. This number is constantly growing, reflecting the recognition of the benefits of kidney transplantation in patients with end-stage renal disease. The transplanted kidney takes over the function of the damaged kidneys and helps to restore the patient's health, offering improved survival, better quality of life, and lower treatment costs compared with regular lifelong dialysis [1–3].

After a kidney transplant, long-term immunosuppression is necessary to prevent rejection of the transplanted kidney. The specific immunosuppressive regimen varies depending on the individual patients and their levels of immunological risk, but typically involves

taking several oral drugs for the rest of the patient's life [4]. The immunosuppressive drugs work by suppressing the kidney recipient's immune system and preventing it from attacking the transplanted kidney [5].

Calcineurin inhibitors (CNIs), including CsA and Tac, are immunosuppressive drugs used extensively in the post-transplantation period to prevent the rejection of the transplanted organ [6,7]. These immunosuppressive agents inhibit the action of calcineurin, an enzyme that activates T-lymphocytes in the immune system, which plays a key role in cell-mediated immunity. However, the use of CNIs has been linked to an increased risk of developing various skin malignancies in renal transplant recipients due to continuous immunosuppression [6]. The increased risk of skin cancer in patients receiving CNI treatment is associated with several pathogenetic mechanisms that are often discussed. These mechanisms include the weakening of the immune system, which is a natural defense mechanism against tumor development and growth. The impact of immunosuppression on the skin can result in a decreased ability to protect against UV radiation and DNA damage. Additionally, calcineurin inhibitors can directly affect skin cells, leading to increased cell proliferation. This increased proliferation of skin cells can contribute to an elevated risk of developing skin cancer. Moreover, patients receiving immunosuppression are more susceptible to infections with oncogenic viruses, further increasing the risk of developing virus-related skin cancer [7,8]. Non-melanoma skin cancers (NMSC), including squamous cell carcinoma (SCC) and basal cell carcinoma (BCC), are the most common malignancies in renal transplant recipients [8,9]. An increased frequency of melanoma has also been reported among renal transplant recipients [8–11].

A limited number of studies have investigated the use of CNIs after kidney transplantation and the potential for skin malignancy development; therefore, we decided to systematically review the available evidence with the objective of comparing the carcinogenic potential of immunosuppressive regimens including CNIs with those that do not include CNIs. Additionally, we aimed to provide the number needed to harm (NNH) for skin malignancies in kidney transplant patients who need to take lifelong immunosuppressive drugs.

The principal aim of our meta-analysis was to compare the incidence of skin malignancies in patients who had undergone renal transplantation treated with CNIs to those treated with other immunosuppressive agents.

To the best of our knowledge, this is the first systematic review and meta-analysis aimed at establishing a correlation between CNI use and the risk of skin malignancies in renal transplant recipients.

2. Materials and Methods

This study was designed to analyze the influence of CNIs, such as CsA and Tac, on the incidence of skin cancer after kidney transplantation. The study compared two therapeutic options used in renal transplant recipients: CNIs (CNIs group) and other immunosuppressants (no CNIs group). This systematic review and meta-analysis has been registered in PROSPERO under the unique identifier "CRD42023396207". As a systematic review and meta-analysis, this study did not require any ethical approval or participant consent.

2.1. Search Terms

The authors followed the PRISMA guidelines to ensure the highest quality of their work [12]. The search was conducted using PubMed, Scopus, and Web of Science databases and was limited to studies published between March 1996 and November 2022. The search strategy was based on the following terms: "Cyclosporine", "Cyclosporin", "Ciclosporin", "Tacrolimus", "calcineurin inhibitors", "CNI", "skin neoplasms", "skin cancers", "skin cancer", "squamous cell cancer", "squamous cell carcinoma", "squamous cell carcinomas", "Squamous Cell Neoplasms", "basal cell carcinoma", "SCC", "BCC", "melanoma", "kidney transplantation", "renal transplantation", "kidney transplant", and "renal transplant". All

of the above-mentioned terms were combined using operators such as "AND" and "OR". All found abstracts were screened for inclusion by two members of the review team (AK and KR) under the supervision of senior authors (TS, MKR, MK, TW, and WMW). The selected abstracts were thoroughly assessed and included in the meta-analysis based on the inclusion criteria.

2.2. Eligibility Assessment

The authors conducted an eligibility assessment for all full-text articles that passed the abstract screening. We included randomized clinical trials, cohort studies, and case-control studies that reported on post-renal transplantation patients and compared the risk of developing melanoma (M) and non-melanoma skin cancer, such as squamous cell and basal cell carcinomas, between those treated with cyclosporine or tacrolimus and those who were treated with immunosuppressants other than CNIs (i.e., CNIs group vs. no CNIs group). We only analyzed articles that had full text and were written in English. The authors excluded all meta-analyses, systematic reviews, studies on pediatric kidney transplants, and otherwise irrelevant studies.

2.3. Data Extraction

Two reviewers recorded relevant data from the selected papers. At least two authors extracted data from each article. In the event of conflicting data, one of the senior authors reviewed the study for further discussion and assistance with the decision regarding the inclusion of data.

2.4. Outcomes of Interest

The following data were extracted from the included studies: publication year, first author, title, type of study, country, follow-up period in years, patient sex, mean or median age of patients at the time of transplantation, transplant period (defined as the range of years during which the kidney transplantation was performed), median time from transplantation to skin malignancy diagnosis in years, sample size (defined as the population analyzed and separated into samples of kidney transplant recipients on CNI therapy and those without CNI therapy), type of skin malignancy diagnosed, including melanoma, non-melanoma skin cancer (NMSC), and total skin cancer in the CNIs and no CNIs groups. The authors adhered to the ethical guidelines and respected patient data ownership. The data used in this meta-analysis were obtained from publicly available literature and were de-identified to ensure patient confidentiality and privacy. Furthermore, the authors have made every effort to comply with the relevant copyright regulations and intellectual property rights while citing and referencing the original sources appropriately.

2.5. Quality Assessment

The quality of the included articles was evaluated using the Cochrane risk-of-bias tool for randomized trials (RoB 2) (The Cochrane Collaboration, 2020, London, UK). Several factors were recorded and measured, such as "Randomization process", "Deviations from the intended interventions", "Missing outcome data", "Measurement of the outcome", and "Selection of the reported result". Each article was evaluated as "high risk", "low risk", or "some concerns".

2.6. Statistical Analysis

Statistical analysis was carried out using R 4.2.2 (R Core Team, 2023) using publicly-available tidyverse and metabin packages. The authors divided the studies into three groups and analyzed the risk of melanoma, non-melanoma skin cancer, and total skin cancer. The relationship between CNI use and skin cancer risk was evaluated using the odds-ratio (as the effect size metric) and corresponding 95% confidence interval. Pooled estimates were obtained using the Mantel-Haenszel method [13–15]. The exact calculation was used for MSC due to presence of cells with zero frequency, as has been recommended [16].

For the heterogeneity variance calculation (tau-squared), the Der-Simonian Laird (1986) estimator was utilized. The Knapp–Hartung adjustment for the CI of the effect was also used, in order to account for between-study heterogeneity [17].

We assessed homogeneity between studies using the I-squared value and Q statistic. Due to low event/trial count, the 95% CI was also reported for the I-squared, as has been recommended [18]. We examined all of the included studies for sources of heterogeneity. As these populations are geographically diverse, the true risk difference may vary, and thus the random-effects model was selected to account for cross-population differences (aside from sampling error).

3. Results

3.1. Article Selection

The primary search resulted in 829 records, and after the removal of duplicates, 769 articles were identified. Among these, 452 were not relevant to our study objective, 215 were case reports, 7 were on pediatric transplants, 59 were not available in English, 21 had no significant data, and 15 were reviews. After screening, 17 articles met the criteria for full-text review. In total, 10 studies were excluded by the authors after reanalysis due to the lack of relevant data. Finally, 7 papers that included a total of 309,551 patients were selected for the meta-analysis (Table 1). The eligibility screening process is depicted in detail in the PRISMA flow diagram (Figure 1).

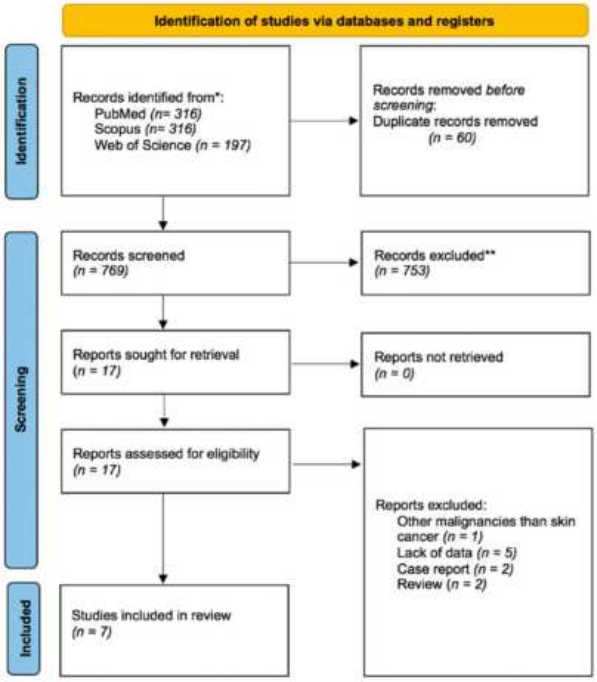

Figure 1. PRISMA flow diagram of the study inclusion process.

Table 1. Characteristics of included studies.

Publication Year	First Author	Title	Study Design (Rct/Cohort /Case-Control)	Country	Sample (n)	Follow-Up in Years	Sex (% Women)	Mean Or Median Age Of Transplantation	Transplant Period	Sample on CNI Therapy (n)	Sample Without CNI Therapy (n)	Sample CNI-MSC (n)	Sample CNI-NMSC (n)	Sample CNI-Total Skin Cancer (n)	Sample No CNI-MSC (n)	Sample No CNI-NMSC (n)	Sample No CNI-Total Skin Cancer (n)	Median Time to Diagnosis in Years
2022	Xiaowei Hao [19]	Skin cancer outcomes and risk factors in renal transplant recipients: Analysis of organ procurement and transplantation network data from 2000 to 2021	Cohort	China	199,564	7.23	39.45	49.49	2000–2014	172,923	26,641	834 (0.48%)	11,791 (6.82%)	12,625 (7.3%)	102 (0.38%)	1636 (6.14%)	1738 (6.52%)	5.84
2017	Mona Ascha [20]	Risk Factors for Melanoma in Renal Transplant Recipients	Cohort	USA	105,174	NS	49.3	49.6	2004–2012	95,818	9356	435 (0.45%)	x	x	53 (0.57%)	x	x	NS
2016	Martina Krasova [21]	Immunosuppressive therapy in the posttransplant period and skin cancer	Cohort	Czech Republic	797	5.3	34.3	48.73	1980–2016	633	164	x	32 (5.06%)	x	x	11 (6.7%)	x	7.97
1996	Bavinck Jan N. Bouwes [22]	The risk of skin cancer in renal transplant recipients in Queensland, Australia. A follow-up study	Cohort	Australia	1098	11.7	62.4	45.9	1969–1994	519	403	x	x	98 (18.89%)	x	x	120 (29.78%)	4.7
2010	Josefina Alberú [23]	Lower Malignancy Rates in Renal Allograft Recipients Converted to Sirolimus-Based, Calcineurin Inhibitor-Free Immunotherapy	RCT	International	830	3.1	29.5	42.6	NS	275	555	3 (1.1%)	22 (8%)	25 (9.1%)	0 (0%)	12 (2.16%)	12 (2.16%)	NS
2015	André Pinho [24]	Non-melanoma skin cancer in Portuguese kidney transplant recipients—incidence and risk factors	Case con-trol	Portugal	288	3.67	34	47	2004–2013	245	23	x	60 (24.49%)	x	x	3 (13.04%)	x	5.35
2012	Hermina C. Wisgerhof [25]	Kidney Transplant Recipients with Cutaneous Squamous Cell Carcinoma Have an Increased Risk of Internal Malignancy	Cohort	Netherlands	1800	11	38	43	1966–2006	549	1171	x	34 (6.19%)	x	x	142 (12.13%)	x	19.4

Abbreviations: CNI, calcineurin inhibitor; MSC, melanoma skin cancer; NMSC, non-melanoma skin cancer; NS, not stated; RCT, randomized controlled trial.

3.2. Article Characteristics

Seven articles were included in the statistical analysis. The chosen articles contained 309,551 renal transplant recipients in Europe, Asia, Australia, and the USA between 1966 and 2016. We stratified data into three subgroups to assess the following outcome measures: "melanoma risk", "non-melanoma skin cancer risk", and "total skin cancer risk".

3.3. Patient Characteristics

The authors selected and included seven articles, and a total of 309,551 patients were analyzed. There were 270,962 patients who were undergoing therapy using CNIs, such as CsA or Tac, and 38,313 patients who were treated using immunosuppressants other than CNIs. The entire dataset for the specified outcome measures included the following: 1427 patients for melanoma risk, 13,743 patients for non-melanoma skin cancer risk, and 14,618 patients for total skin cancer risk.

3.4. Melanoma Risk

The meta-analysis of outcomes presented by Alberu et al., Ascha et al., and Hao et al. [19,20,23] prove a statistically significant association between the use of CNIs and an increased risk of melanoma (OR 1.09; 95% CI: 0.25–4.74; $p < 0.01$). The results are presented in Figure 2. The NNH for melanoma risk and CNI treatment was 1541.1.

3.5. Non-Melanoma Skin Cancer Risk

The analysis of non-melanoma skin cancer risk based on five studies (Alberu et al., Hao et al., Krasova et al., Pinho et al., and Wisgerhof et al. [19,21,23–25]) revealed a statistically significant difference with a lower risk of cancer development in the no CNIs group (OR 1.16; 95% CI: 0.41–3.26; $p < 0.01$). The data are shown in Figure 3. The NNH for non-melanoma cancer risk was 330.7.

3.6. Total Skin Cancer Risk

Total skin cancer risk analysis included four articles (Alberu et al., Bouwes et al., Hao et al., [19,22,23]). Patients who were taking CNIs had higher total skin cancer risk (OR 1.28; 95% CI: 0.10–16.28; $p < 0.01$). The results are presented in Figure 4. The NNH for total cancer risk was 567.8.

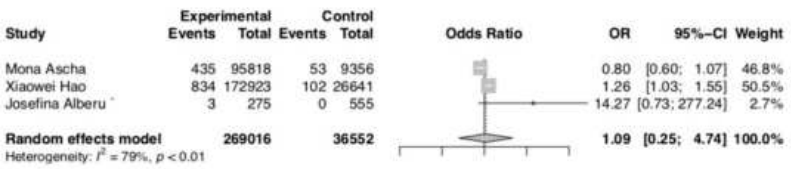

Figure 2. Melanoma risk [19,20,23].

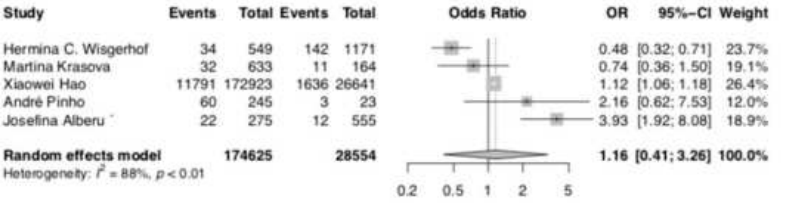

Figure 3. Non-melanoma skin cancer risk [19,21,23–25].

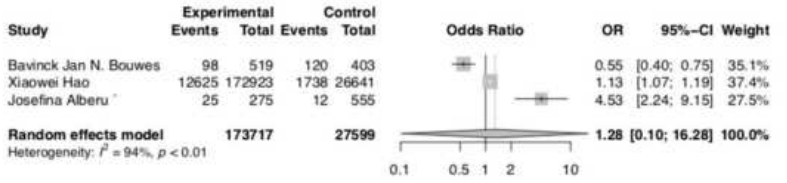

Figure 4. Total skin cancer risk [19,22,23].

3.7. Quality Assessment

The risk of bias was low in certain aspects of the study, such as "Missing outcome data" and "Measurement of the outcome," but there were some concerns in others, such as "Randomization process" and "Deviations from the intended interventions". The risk of bias for "Selection of the reported result" was high. The overall quality of the included articles is evaluated in Figure 5.

Figure 5. Quality assessment—Cochrane risk-of-bias tool for randomized trials (RoB 2) [19–25].

4. Discussion

According to the "Renal Association Clinical Practice Guideline in Post-Operative Care in the Kidney Transplant Recipient", CNI treatment should be started at the beginning of transplantation and continued until the graft is fully functional. Lifelong immunosuppressive therapy is required to prevent graft rejection and ensure proper functioning; however, studies have shown that CNI treatment can increase the risk of skin cancer due to the promotion of unrestricted cell division [26–28]. The potential mechanisms behind the increased risk of skin cancer with CNI therapy include the inhibition of DNA repair, the modification of immune function, and the suppression of the p53 protein [28]. Non-melanoma skin cancer, such as squamous cell carcinoma and basal cell carcinoma, is the most common type of skin malignancy affecting kidney transplant recipients [29–32].

We performed a statistical analysis on three parameters: melanoma risk, non-melanoma risk, and total cancer risk. All of them showed a statistically significant difference between a group of patients who were receiving CNIs and a group of patients who received alternative immunosuppressants and did not receive CNIs in the parameters studied. Melanoma risk was higher in the group of patients who were treated with CNIs (CsA and Tac) compared to the other group (OR 1.09; 95% CI: 0.25–4.74; $p < 0.01$). Non-melanoma skin cancer risk (OR 1.16; 95% CI: 0.41–3.26; $p < 0.01$) and total skin cancer risk (OR 1.28; 95% CI: 0.10–16.28; $p < 0.01$) were also slightly higher in the group of patients who had undergone renal transplantation treated with CNIs. Our findings, which are based on a large, pooled patient group of more than 300,000 kidney transplant recipients, indicate that permanent exposure to CNI treatment increases the risk of skin cancer. However, compared to other immunosuppressive drugs, this effect is not as significant as we initially expected.

This association has been reported before; however, in contrast to previous studies [19–25], we were able to demonstrate statistically significant differences in all three parameters of melanoma risk, non-melanoma skin cancer risk, and total skin cancer risk. Our results suggest that the increased risk of skin cancer associated with CNI treatment may not be as widespread an issue as previously thought. In addition, we calculated the number needed to harm (NNH)

parameter, which represents the number of patients that must be treated with CNIs for one individual to develop skin cancer [33]. We believe that this parameter most accurately illustrates the real risk related to CNI usage in this patient group in the context of skin cancer. The number needed to harm values were 1541.4 for melanoma risk, 330.7 for non-melanoma skin cancer risk, and 567.8 for total cancer risk. This means that every six hundredth patient taking CNI during the course of immunosuppression develops skin cancer (mainly basal and squamous cell carcinoma). Melanoma, with an NNH approaching 1541, is not a real threat to long-term CNI users. Our meta-analysis, which included more than 309,000 kidney transplant recipients across the included studies, is much larger than previous meta-analyses investigating the effect of CNIs on skin malignancies, and, to our knowledge, our study is the only one performed on a group of kidney recipients. This study takes into account research conducted on multiple continents and in different age groups, which reduces the influence of additional factors (such as sunlight exposure), as compared to previous studies.

An NNH of 330 for non-melanoma skin malignancy associated with long-term immunotherapy using drugs from the group of CNIs leads to a very practical conclusion. This means that physicians dealing with kidney transplant recipients who are on long-term CNI treatment should carefully monitor patients for any signs of skin cancer and educate them on the importance of sun protection measures. Further research is needed to explore the underlying mechanisms of this association and to develop strategies to mitigate the risk of skin cancer in this patient population.

Our study has several important limitations. First, although a comprehensive literature search was conducted, the available literature on this topic is limited, and only a small number of relevant studies were found. Additionally, some of the studies included a variety of immunosuppressive drug regimens, making it difficult to isolate the effects of CNI monotherapy, and we were unable to include all data from the selected studies in our systematic review. Furthermore, some studies did not include and/or listed separately all types of skin malignancies (melanoma, squamous cell carcinoma, or basal cell carcinoma). Moreover, due to the variability in the nature of the included studies—such as differences in patient numbers, locations, and other additional factors which might increase the risk of skin cancers (such as high lifetime exposure to ultraviolet radiation from the sun, prior scars, chronic wounds, actinic keratosis, paler skin, Bowen's disease, arsenic exposure, radiation therapy, tobacco smoking, poor immune system function, prior basal cell carcinoma, or HPV infection) [34,35]—there is a lack of uniformity that hinders the ability to draw strong conclusions from the systematic review. The selected studies encompassed a range of methodologies and characteristics, making it challenging to establish consistent patterns or generalize the findings. As a result, the diverse nature of the included studies limits the extent to which we can confidently interpret the results of the systematic review.

Another limitation of our study is the lack of specification regarding whether the patient is taking CsA or Tac, as well as the absence of information regarding other potential confounding factors; an example of this is the concurrent use of azathioprine, which has a higher potential carcinogenesis than CNIs [36]. This implies that the NNH estimates we have acquired must undergo verification by analyzing aggregated data obtained from transplant registries or alternative sources. It is evident that further measures are required to ensure their validity on a broader scale.

Despite these limitations, the strength of our meta-analysis lies in our profound analysis of available relevant studies, strict inclusion criteria, and the integration of these studies to formulate a clinically important practical consensus. Due to the scarcity of studies examining the relationship between CNIs and skin cancer after kidney transplantation, the authors decided to provide the most up-to-date and complete conclusions based on our results and the available literature (see Section 5). To the best of our knowledge, the study is also unique and is the most precise meta-analysis that aims to establish a correlation between exposure to CNIs and the risk of skin cancer in renal transplant recipients. Another reason to study the potential relationship between CNIs and skin cancer is the increasing number of kidney transplant recipients and long-term survivors with lifetime CNI usage

globally. Acknowledging the delayed consequences of therapy may be helpful in selecting therapy regimens and setting up necessary follow-up skin recommendations for patients on long-term CNI therapy.

Long-term immunosuppression in kidney transplant recipients has a beneficial effect on survival; however, it is associated with significant risks of skin cancer [37,38]. According to previous research, the risk of developing malignancies is four times higher in individuals who have undergone transplantation compared to the general population. Consequently, most international clinical guidelines recommend regular screening for skin, cervical, and colorectal cancer during the post-transplant period. It is therefore obligatory to inform patients and educate them on self-examination techniques and to encourage them to make frequent follow-up visits. Guidelines recommend that kidney transplant recipients should be screened for skin cancer occurrence at least twice a year for five years after transplantation [26,27,37,39–42]. Considering the potential for delayed development of skin malignancies in patients receiving calcineurin inhibitors (CNIs), we would recommend lifelong and continuous surveillance of the skin.

5. Conclusions

We showed that kidney transplant recipients undergoing long-term CNI therapy exhibit a statistically higher incidence of skin cancer compared to patients receiving alternative immunosuppressive treatments. However, the observed difference does not appear to have significant clinical implications when compared to immunosuppressive regimens that do not include CNIs. The risk of skin melanoma is also elevated, albeit to a considerably lesser extent, which may be disregarded in a clinical context. Early detection of non-melanoma skin cancers and melanoma is crucial for achieving favorable treatment outcomes. Detecting these cancers at an early stage allows for a more conservative therapeutic approach, minimizing the need for extensive interventions and improving long-term prognosis. Therefore, regular skin examinations and patient education on self-examination techniques are very important. It is also crucial to individualize the schedule for follow-up screenings based on risk factors and the need for a multidisciplinary approach involving dermatologists. We propose the implementation of lifelong skin monitoring sessions for patients with transplanted kidneys who are on long-term immunosuppression, including regimens with CNI. Furthermore, we strongly advocate for patient education regarding this undesired effect of CNIs to enhance awareness and facilitate early detection of skin lesions by the patients themselves.

Additionally, in order to obtain a more comprehensive understanding of the topic, we recommend conducting further meta-analyses that take into account specific subgroups of patients receiving distinct immunosuppressive drugs. Unfortunately, this is currently unfeasible due to insufficient data in the available studies and challenges associated with data extraction. Our meta-analysis encountered numerous limitations and obstacles, and the estimated outcomes and assessments should be verified through the analysis of aggregated data from transplant registries or other accessible sources. It is evident that additional efforts are required to ensure the validity and objectivity of the findings on a larger scale.

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References

1. Haberal, M.; Boyvat, F.; Akdur, A.; Kırnap, M.; Özçelik, Ü.; Yarbuğ Karakayalı, F. Surgical complications after kidney transplantation. *Exp. Clin. Transpl.* **2016**, *14*, 587–595.
2. Silva, S.B.; Caulliraux, H.M.; Araújo, C.A.; Rocha, E. Cost comparison of kidney transplant versus dialysis in Brazil. *Cad. Saude Publica* **2016**, *32*, S0102-311X2016000605005. [CrossRef] [PubMed]
3. Garcia, G.G.; Harden, P.; Chapman, J. The World Kidney Day Steering Committee 2012. The global role of kidney transplantation. *J. Nephropathol.* **2012**, *1*, 69–76. [CrossRef] [PubMed]
4. Cheung, C.Y.; Tang, S.C.W. Personalized immunosuppression after kidney transplantation. *Nephrology* **2022**, *27*, 475–483. [CrossRef]
5. Legendre, C.; Zuber, J.; Anglicheau, D.; Le Quintrec, M.; Martinez, F.; Mamzer-Bruneel, M.F.; Thervet, E. Immunosuppression en transplantation rénale [Immunosuppression in kidney transplantation]. *Ann. Urol. (Paris)* **2007**, *41*, 276–284. [CrossRef]
6. Parlakpinar, H.; Gunata, M. Transplantation and immunosuppression: A review of novel transplant-related immunosuppressant drugs. *Immunopharmacol. Immunotoxicol.* **2021**, *43*, 651–665. [CrossRef]
7. Tönshoff, B. Immunosuppressants in organ transplantation. *Handb. Exp. Pharmacol.* **2020**, *261*, 441–469. [CrossRef]
8. Robbins, H.A.; Clarke, C.A.; Arron, S.T.; Tatalovich, Z.; Kahn, A.R.; Hernandez, B.Y.; Paddock, L.; Yanik, E.L.; Lynch, C.F.; Kasiske, B.L.; et al. Melanoma risk and survival among organ transplant recipients. *J. Investig. Dermatol.* **2015**, *135*, 2657–2665. [CrossRef]
9. Clarke, C.A.; Robbins, H.A.; Tatalovich, Z.; Lynch, C.F.; Pawlish, K.S.; Finch, J.L.; Hernandez, B.Y.; Fraumeni, J.F., Jr.; Madeleine, M.M.; Engels, E.A. Risk of Merkel cell carcinoma after solid organ transplantation. *J. Natl. Cancer Inst.* **2015**, *107*, dju382. [CrossRef]
10. Euvrard, S.; Kanitakis, J.; Claudy, A. Skin cancers after organ transplantation. *N. Engl. J. Med.* **2003**, *348*, 1681–1691. [CrossRef]
11. Aguiar, B.; Santos Amorim, T.; Romãozinho, C.; Santos, L.; Macário, F.; Alves, R.; Campos, M.; Mota, A. Malignancy in kidney transplantation: A 25-year single-center experience in Portugal. *Transplant. Proc.* **2015**, *47*, 976–980. [CrossRef]
12. Page, M.J.; McKenzie, J.E.; Bossuyt, P.M.; Boutron, I.; Hoffmann, T.C.; Mulrow, C.D. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *Int. J. Surg.* **2021**, *88*, 105906. [CrossRef]
13. Mantel, N.; Haenszel, W. Statistical Aspects of the Analysis of Data from Retrospective Studies of Disease. *J. Natl. Cancer Inst.* **1959**, *22*, 719–748.
14. Robins, J.; Breslow, N.; Greenland, S. Estimators of the Mantel-Haenszel variance consistent in both sparse data and large-strata limiting models. *Biometrics* **1986**, *42*, 311–323. [CrossRef]
15. Greenland, S.; Robins, J.M. Estimation of a common effect parameter from sparse follow-up data. *Biometrics* **1985**, *41*, 55–68. [CrossRef]
16. Fleiss, J.L. The statistical basis of meta-analysis. *Stat. Methods Med. Res.* **1993**, *2*, 121–145. [CrossRef]
17. Knapp, G.; Hartung, J. Improved tests for a random effects meta-regression with a single covariate. *Stat. Med.* **2003**, *22*, 2693–2710. [CrossRef] [PubMed]
18. Thorlund, K.; Imberger, G.; Johnston, B.C.; Walsh, M.; Awad, T.; Thabane, L.; Gluud, C.; Devereaux, P.J.; Wetterslev, J. Evolution of heterogeneity (I2) estimates and their 95% confidence intervals in large meta-analyses. *PLoS ONE* **2012**, *7*, e39471. [CrossRef] [PubMed]
19. Hao, X.; Lai, W.; Xia, X.; Xu, J.; Wu, Y.; Lv, C.; Meng, Q.; Lv, K.; Huang, S.; Luo, Z.; et al. Skin cancer outcomes and risk factors in renal transplant recipients: Analysis of organ procurement and transplantation network data from 2000 to 2021. *Front. Oncol.* **2022**, *12*, 1017498. [CrossRef] [PubMed]
20. Ascha, M.; Ascha, M.S.; Tanenbaum, J.; Bordeaux, J.S. Risk Factors for melanoma in renal transplant recipients. *JAMA Dermatol.* **2017**, *153*, 1130–1136. [CrossRef] [PubMed]
21. Krásová, M.; Sečníková, Z.; Göpfertová, D.; Hercogová, J.; Viklický, O.; Jůzlová, K.; Jiráková, A.; Šmerhovský, Z. Immunosuppressive therapy in the posttransplant period and skin cancer. *Dermatol. Ther.* **2016**, *29*, 433–436. [CrossRef]
22. Bouwes Bavinck, J.N.; Hardie, D.R.; Green, A.; Cutmore, S.; MacNaught, A.; O'Sullivan, B.; Siskind, V.; Van Der Woude, F.J.; Hardie, I.R. The risk of skin cancer in renal transplant recipients in Queensland, Australia. A follow-up study. *Transplantation* **1996**, *61*, 715–721. [CrossRef]
23. Alberú, J.; Pascoe, M.D.; Campistol, J.M.; Schena, F.P.; Rial Mdel, C.; Polinsky, M.; Neylan, J.F.; Korth-Bradley, J.; Goldberg-Alberts, R.; Maller, E.S. Sirolimus CONVERT Trial Study Group. Lower malignancy rates in renal allograft recipients converted to sirolimus-based, calcineurin inhibitor-free immunotherapy: 24-month results from the CONVERT trial. *Transplantation* **2011**, *92*, 303–310. [CrossRef] [PubMed]
24. Pinho, A.; Gouveia, M.; Cardoso, J.C.; Xavier, M.M.; Vieira, R.; Alves, R. Non-melanoma skin cancer in Portuguese kidney transplant recipients—Incidence and risk factors. *An. Bras. Dermatol.* **2016**, *91*, 455–462. [CrossRef]
25. Wisgerhof, H.C.; Wolterbeek, R.; de Fijter, J.W.; Willemze, R.; Bouwes Bavinck, J.N. Kidney transplant recipients with cutaneous squamous cell carcinoma have an increased risk of internal malignancy. *J. Investig. Dermatol.* **2012**, *132*, 2176–2183. [CrossRef] [PubMed]
26. Baker, R.J.; Mark, P.B.; Patel, R.K.; Stevens, K.K.; Palmer, N. Renal association clinical practice guideline in post-operative care in the kidney transplant recipient. *BMC Nephrol.* **2017**, *18*, 174. [CrossRef]
27. Smith, A.; Niu, W.; Desai, A. The effect of conversion from a calcineurin inhibitor to sirolimus on skin cancer reduction in post-renal transplantation patients. *Cureus* **2017**, *9*, e1564. [CrossRef]

28. Wisgerhof, H.C.; Edelbroek, J.R.; de Fijter, J.W.; Haasnoot, G.W.; Claas, F.H.; Willemze, R.; Bavinck, J.N. Subsequent squamous- and basal cell carcinomas in kidney-transplant recipients after the first skin cancer: Cumulative incidence and risk factors. *Transplantation* **2010**, *89*, 1231–1238. [CrossRef]
29. Burke, M.T.; Isbel, N.; Barraclough, K.A.; Jung, J.W.; Wells, J.W.; Staatz, C.E. Genetics and nonmelanoma skin cancer in kidney transplant recipients. *Pharmacogenomics* **2015**, *16*, 161–172. [CrossRef] [PubMed]
30. Ramsay, H.M.; Fryer, A.A.; Reece, S.; Smith, A.G.; Harden, P.N. Clinical risk factors associated with nonmelanoma skin cancer in renal transplant recipients. *Am. J. Kidney Dis.* **2000**, *36*, 167–176. [CrossRef]
31. Sheil, A.G. Cancer in renal allograft recipients in Australia and New Zealand. *Transplant. Proc.* **1977**, *9*, 1133–1136.
32. Walder, B.K.; Robertson, M.R.; Jeremy, D. Skin cancer and immunosuppression. *Lancet* **1971**, *2*, 1282–1283. [CrossRef] [PubMed]
33. Suchmacher, M.; Geller, M. *Practical Biostatistics, Chapter 2—Determination of Association Strength between an Exposure Factor and an Event in Observational Studies*; Academic Press: Cambridge, MA, USA, 2012; pp. 19–29. ISBN 9780124157941. Available online: https://www.sciencedirect.com/science/article/pii/B9780124157941000021 (accessed on 6 March 2023).
34. Karczewski, M.; Stronka, M.; Karczewski, J.; Wiktorowicz, K. Skin cancer following kidney transplantation: A single-center experience. *Transplant. Proc.* **2011**, *43*, 3760–3761. [CrossRef] [PubMed]
35. Gandhi, S.A.; Kampp, J. Skin Cancer Epidemiology, Detection, and Management. *Med. Clin. N. Am.* **2015**, *99*, 1323–1335. [CrossRef] [PubMed]
36. Basal and Squamous Cell Skin Cancer Risk Factors. American Cancer Society. 2009. Available online: www.cancer.org/cancer/types/basal-and-squamous-cell-skin-cancer/causes-risks-prevention/risk-factors.html (accessed on 10 January 2023).
37. Jiyad, Z.; Olsen, C.M.; Burke, M.T.; Isbel, N.M.; Green, A.C. Azathioprine and Risk of Skin Cancer in Organ Transplant Recipients: Systematic Review and Meta-Analysis. *Am. J. Transplant.* **2016**, *16*, 3490–3503. [CrossRef]
38. Cordaro, A.; Dobbs, T.D.; Gibson, J.A.; Whitaker, S.; Whitaker, I.S. Skin cancer screening in organ transplant centres in the United Kingdom: A national survey. *Eur. J. Dermatol.* **2020**, *30*, 372–376. [CrossRef]
39. Garrett, G.L.; Blanc, P.D.; Boscardin, J.; Lloyd, A.A.; Ahmed, R.L.; Anthony, T.; Bibee, K.; Breithaupt, A.; Cannon, J.; Chen, A.; et al. Incidence of and risk factors for skin cancer in organ transplant recipients in the United States. *JAMA Dermatol.* **2017**, *153*, 296–303. [CrossRef]
40. Manickavasagar, R.; Thuraisingham, R. Post renal-transplant malignancy surveillance. *Clin. Med. (Lond.)* **2020**, *20*, 142–145. [CrossRef]
41. EBPG Expert Group on Renal Transplantation. European best practice guidelines for renal transplantation. Section IV: Longterm management of the transplant recipient. *Nephrol. Dial. Transplant* **2002**, *17* (Suppl. 4), 1–67. [CrossRef]
42. American Society of Transplantation. Guidelines for Post-Kidney Transplant Management in the Community Setting. AST. 2009. Available online: www.myast.org/guidelines-post-kidney-transplant-managementcommunity-setting-0 (accessed on 15 January 2023).

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Melanoma incidence in 17,252 organ transplant recipients in Poland between 2010 and 2022

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Introduction. Numerous studies indicate an increased incidence of skin malignancies among organ transplant recipients. Melanoma pose a significant threat to post-transplant recipients, leading to considerable mortality. This study explores the incidence of melanoma after 17,252 organ transplantations in Poland over the past 13 years.

Materials and methods. The data on the occurrence of melanoma in patients after renal, heart, or liver transplantation were obtained from the National Health Fund, encompassing individuals who underwent kidney, heart, or liver transplantation between 2010 and 2022. The analysis focused on skin melanoma (C43).

Results. The study examined skin melanoma in renal (12,250 cases), liver (3,584 cases), and heart (1,418 cases) transplant recipients over a period of thirteen years. Melanoma incidence slightly increased in renal recipients (1-year cumulative incidence 0.016% *vs.* 0.007%, $p = 0.024$; 5-year cumulative incidence 0.131% *vs.* 0.040% $p < 0.001$; the 10-year cumulative incidence 0.213% *vs.* 0.09, $p < 0.001$). In liver transplant recipients there is a non-significant difference 1-year after transplantation (cumulative incidence 0.03% *vs.* 0.01%, $p = 0.337$) but after 5 and 10 years the difference between the two groups remains statistically significant (5-year cumulative incidence 0.14% *vs.* 0.04%, $p < 0.014$; the 10-year cumulative incidence 0.14% *vs.* 0.09%, $p < 0.001$). In heart transplant recipients, a paradoxical reduction in incidence was observed compared to the general population (1-year cumulative incidence 0% *vs.* 0.01%, $p = 0.317$; 5-year cumulative incidence 0.07% *vs.* 0.04%, $p = 0.049$; the 10-year cumulative incidence 0.07% *vs.* 0.09, $p < 0.001$).

Conclusions. The incidence of melanoma increases in kidney transplant recipients over the first 10 years post-transplant, with a peak between 4 to 7 years. For heart and liver transplant recipients, melanoma cases occur within the initial 5 years post-transplant, and no new cases were recorded afterward. The long-term surviving kidney, heart, and liver transplant recipients show a steady rise in new cases over time. Our study, based on a thorough analysis of data from the National Health Fund, confirms the link between an elevated risk of melanoma in organ transplant recipients.

Key words: skin cancer, melanoma, transplant recipients, transplantation

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Introduction

In 2023, according to the National Health Fund, a total 1,910 organ transplants were performed in Poland, including 1,055 kidney transplants, 550 liver transplants, and 178 heart transplants, marking an unprecedented achievement in the country's medical history [1]. This notable increase surpassed previous numbers, such as 1,608 organ transplants in 2012 [2]. The global prevalence of organ transplants has been steadily rising, reaching hundreds of thousands annually.

Organ transplantation, hailed as the sole long-term curative treatment for end-stage renal, heart, or liver disease, introduces complex lifelong therapy for recipients. The lifelong immunosuppressive treatment necessary for adequate graft function makes recipients susceptible to various diseases, prominently increasing the risk of cancer. Melanoma, though comprising only 4% of cutaneous malignancies, contributes to 80% of skin cancer deaths in the general population, underscoring its significance among both transplant and non-transplant individuals [3].

The results of available studies show that transplant recipients face a 1,5- to 8-fold increased risk of melanoma compared to the general population, depending on the studied population [4–6], but the risk of developing melanoma consistently increases in all presented data over the time since transplantation.

Data from different European studies also show significant diversity in the risk of neoplasia despite a similar geographical latitude, indicating additional risk factors for the occurrence of cancer, such as genetic predispositions, the influence of applied treatment, or the frequency of human papillomavirus (HPV) infection [7, 8]. Unfortunately, despite numerous works, there is a lack of epidemiological studies based on a large number of patients, especially regarding the frequency of melanoma, which would help in a precise assessment of the real risk of skin cancer in the transplant recipient group.

This report explores the incidence of melanoma after organ transplantation in Poland over the past 13 years (2010–2022), providing insights into the challenges and risks encountered by transplant recipients. This is the largest analysis performed on that particular subject in Poland so far. The study is based on a National Health Fund dataset (public health insurance governmental agency), which provides the most accurate information on actual health incidents for all Polish citizens.

Materials and methods

The data on the occurrence of melanoma in patients after renal, heart, or liver transplantation were obtained from the National Health Fund. The dataset includes patients who underwent renal, heart, or liver transplantation between 2010 and 2022, and it was used to identify a cohort of patients with a diagnosis of melanoma based on any inpatient or outpatient claim associated with an International Classification of Diseases, 10th Revision, Clinical Modification (ICD-10-CM) code for melanoma (C43.0–C43.9).

The information is presented through distinct sets of diagrams, illustrating melanoma (C43) in recipients of the most commonly transplanted organs in Poland – specifically, in renal transplant recipients, liver transplant recipients, and heart transplant recipients. Exclusion criteria included a history of previous organ transplantation and transplantation of more than one of the mentioned organs. Differences in the occurrence of melanoma skin cancer are presented in the diagrams. It is important to note that diagrams related to each specific patient group use a consistent percentage scale for uniform data presentation. To investigate the association between two categorical variables, analytical methods, including Fisher's exact test and the two-sample test for equality of proportions (applied without a continuity correction) were employed. An alpha level ($\alpha = 0.05$) was chosen as the criterion for determining statistical significance. Analyses were conducted using the R Statistical language (version 4.3.1; R Core Team, 2023) on Windows 10 Pro 64 (build 19045).

Based on data obtained from the National Health Fund, we calculated the cumulative incidence rate of melanoma, coded as C43, among organ transplant (Tx) recipients compared to a control population over a 1-, 5-, and 10-year follow-up period. The dataset for this time frame (between 2010 and 2020) was created using information acquired from the National Cancer Registry [9].

Results

The cumulative incidence rate of melanoma, coded as C43, among renal transplant (Tx) recipients compared to a control population over a 1-, 5-, and 10-year follow-up period provided an insightful perspective into the risk stratification associated with this malignancy post-transplantation.

Renal Tx recipients vs. *control population*

The analysis covered 12,250 renal transplant recipients (2010–2022), examining the risk of melanoma skin cancer. The histogram (fig. 1) displays the percentage of melanoma cases among living renal transplant recipients. A slight increase is observed in the fourth to seventh years (0.04% and 0.07%, respectively), followed by a decrease in subsequent years. No cases are reported after the tenth year.

Table I presented the cumulative incidence rates of melanoma (C43) in patients post renal Tx as opposed to a control population over 1-, 5-, and 10-year intervals, allowing for a comparative oncological risk assessment. The observed trend in table I suggests that renal transplant recipients exhibited a higher cumulative incidence of melanoma skin cancer over time when compared to the general population. This elevated risk could be attributed to the immunosuppressive regimens required to maintain graft function, which can reduce the efficacy of the immune system to detect and eliminate malignant

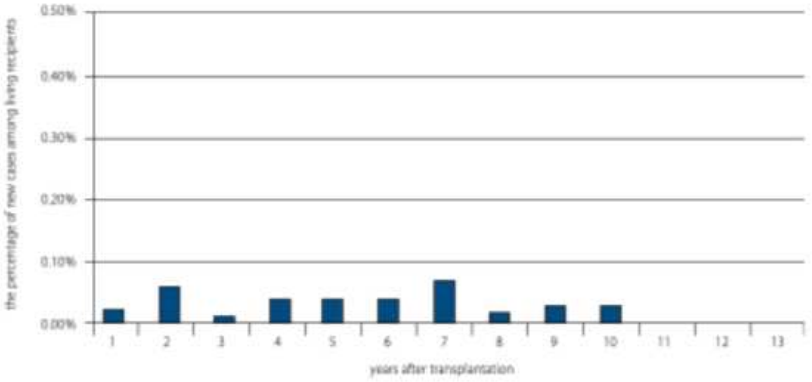

Figure 1. Melanoma in renal transplant recipients

Table I. Cumulative incidence rate of melanoma (C43) over time in patients with renal Tx and control population

Follow-up	Stratification by Tx		p value[b]
	yes[a] N_1 = 12,205	no[a] N_2 = 37.75 mln	
1 yr.	2 (0.02%)	2,660 (0.01%)	0.024
5 yr.	16 (0.13%)	15,092 (0.04%)	<0.001
10 yr.	26 (0.21%)	34,313 (0.09%)	<0.001

N – population size; n – incidence rate of melanoma; [a] – n (%); [b] – two-sample test for equality of proportions

cells. The significantly higher incidence rates in the renal transplant recipients highlighted the interplay between immunosuppression and carcinogenesis.

In the immediate 1-year follow-up, the incidence of melanoma in the renal transplant cohort was 0.016% (2 cases *per* 12,205 patients), which was statistically higher (p = 0.024) than the 0.007% (2,660 cases *per* 37.75 million) observed in the general population. The 5-year cumulative incidence notably increased in the transplant recipients to 0.131% (16 cases *per* 12,205 patients), with a further amplified contrast to the control population's 0.040% (1,592 cases *per* 37.75 million), a difference that was highly significant (p < 0.001). At 10-year, the incidence in the transplant group further escalated to 0.213% (26 cases *per* 12,205 patients), while the control population incidence was 0.091% (34,313 cases *per* 37.75 million), again with a statistically significant difference (p < 0.001).

Liver Tx recipients vs. *control population*

The analysis encompassed 3,584 liver transplant recipients, investigating the risk of melanoma skin cancer. The histogram (fig. 2) illustrates the percentage of melanoma cases among living liver transplant recipients at different intervals post-transplant. The data reveals fluctuations, reaching a peak of 0.12% in the third year, while the other years have either minimal or zero reported cases. Notably, no cases are documented

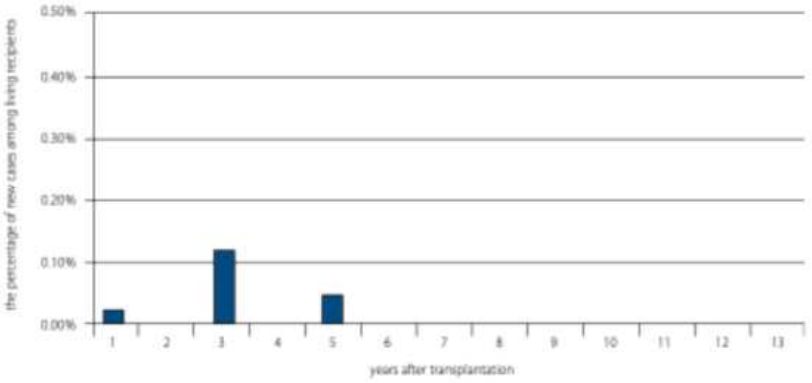

Figure 2. Melanoma in liver transplant recipients

Table II. Cumulative incidence rate of melanoma (C43) over time in patients with liver Tx and control population

Follow-up	Stratification by Tx		p value[a]
	yes*, N_1 = 3,584	no^, N_2 = 37.75 mln	
1 yr.	1 (0.03%)	2,660 (0.01%)	0.337[†]
5 yr.	5 (0.14%)	15,092 (0.04%)	0.014
10 yr.	5 (0.14%)	34,313 (0.09%)	<0.001

N – population size; n – incidence rate of melanoma; [a] – n (%); [b] – two-sample test for equality of proportions; [†] – Fisher's exact test

from the fourth to the thirteenth-year post-transplant. This data effectively portrays the patterns in melanoma incidence among liver transplant recipients over a thirteen-year period.

Table II presented the cumulative incidence rates of melanoma (C43) in patients post liver Tx as opposed to a control population over 1-, 5-, and 10-year intervals, allowing for a comparative oncological risk assessment.

In the 1-year follow-up, there was a single case of melanoma (0.028%) among the 12,205 liver Tx patients, compared to a 0.007% incidence (2,660 cases) within the control population of 37.75 million. The p value of 0.337 indicated no significant difference in the melanoma incidence rate between the liver Tx cohort and the general population at this interval. At the 5-year milestone, the cumulative incidence in liver Tx patients slightly increased to 0.140% (5 cases out of 12,205 patients), which was statistically higher than the control group's 0.040% incidence (1,592 cases out of 37.75 million), with a p-value of 0.014. By the 10-year follow-up, the incidence rate remained at 0.140% (5 cases *per* 12,205 patients) in the liver Tx group, which is intriguing as it did not increase from the 5-year mark. In contrast, the control group's incidence raised to 0.091% (34,313 cases *per* 37.75 million), with the difference between the two groups remaining statistically significant ($p < 0.001$).

Heart Tx recipients vs. control population

The assessment of non-melanoma skin cancer risk involved 1,418 heart transplant recipients. During the initial three years post-transplant, no new cases of melanoma were reported. However, in the fourth year post-transplant, a slight increase in the percentage of cases was observed, reaching 0.16%. From the fifth to the thirteenth year, no new cases were recorded. This histogram (fig. 3) depicts a minimal percentage of melanoma cases among the population of heart transplant recipients in the years following the procedure. Table III delineated the cumulative incidence rate of melanoma (C43) in heart Tx recipients compared with a control population over a 1-, 5-, and 10-year follow-up period.

At 1-year, there were no reported cases of melanoma (0%) among the 1,408 heart Tx recipients, in contrast to the control population's 0.007% incidence (2,660 cases out of 37.75 million). The $p = 0.317$ indicated no statistically significant difference between the groups, which could be due to the relatively short period post-transplantation, not allowing sufficient time for melanoma development or detection. By the 5-year follow-up, the cumulative incidence of melanoma in heart Tx patients was recorded at 0.071% (1 case out of 1,408 patients), which was statistically higher than the control group's incidence of 0.040% (1,592 cases out of 37.75 million), with a p-value of 0.049. The 10-year data revealed the incidence in the heart Tx cohort remained at 0.071% (1 case *per* 1,408 patients), without an increase from the 5-year incidence. This was in contrast to the control population's incidence, which rose to 0.091% (34,313 cases per 37.75 million), with the difference between the groups remaining statistically significant ($p = 0.001$), this time higher in the control group.

Discussion

Melanoma after organ transplantation results in substantial mortality [10, 11]. Several studies have examined the risk of skin melanoma after transplantation, demonstrating

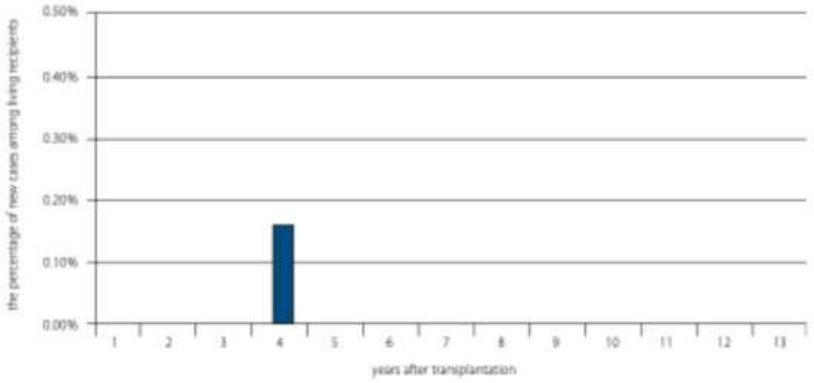

Figure 3. Melanoma in heart transplant recipients

Table III. Cumulative incidence rate of melanoma (C43) over time in patients with heart Tx and control population

Follow-up	Stratification by Tx		p value[a]
	yes[a], N_1 = 1408	no[a], N_2 = 37.75 mln	
1 yr.	0 (0%)	2,660 (0.01%)	0.317[c]
5 yr.	1 (0.07%)	15,092 (0.040%)	0.049
10 yr.	1 (0.07%)	34,313 (0.09%)	0.001

N – population size; n – incidence rate of melanoma; [a] – n (%); [b] – two-sample test for equality of proportions; [c] – Fisher's exact test

a broad and diversified range of the presented increase in the risk of incidence. This raises many questions regarding the scale of this phenomenon in Poland. Studies available for the Polish population describe individual cases conducted on a small group of individuals, or pertain to past times when immunosuppressive treatment often differed from the currently used protocols [4, 12–15].

Our study aimed to reanalyze the potential connection between organ transplant recipients in Poland and the prevalence of melanoma. The authors conducted an analysis of data from the National Health Fund, revealing the occurrence of melanoma in the three most common groups on life-long immunosuppressive therapy:

- renal transplant recipients,
- liver transplant recipients, and
- heart transplant recipients.

Cases of melanoma were recorded only within the first 10 years after renal transplantation, and the cumulative risk of developing melanoma in this period was 0.21%, while the population incidence in this range of time, according to data from the National Cancer Registry, was 0.09%. This suggested a sustained and growing divergence in the risk profile for melanoma between the two groups, possibly attributable to chronic immunosuppressive therapy, which although facilitating survival may contribute to the accumulation of oncogenic mutations and the growth of malignant cells by limiting the body's natural antitumor immune responses.

Melanoma cases in liver transplant recipients were reported only in the first 5 years (cumulative risk 0.14%). This statistically significant difference suggests the potential impact of the post-transplant condition, including the immunosuppressive therapy necessary to prevent liver graft rejection, on the risk of developing melanoma. By the 10-year follow-up, the incidence rate remained at the same level, which is intriguing as it did not increase from the 5-year mark. The stable incidence rate in the liver Tx cohort over the 5 to 10-year period might suggest a plateau effect in the risk of melanoma post-transplant, indicating that the highest risk period may be within the first five years post-transplant. These findings suggest that liver Tx patients have an increased cumulative incidence of melanoma when compared to the general population, particularly evident beyond the 1-year post-transplant period, likely influenced by immunomodulatory effects of long-term immunosuppression, which may reduce immunosurveillance, and allow for the development and progression of melanoma.

Heart transplant recipients in Poland also received a melanoma diagnosis only within 5 years of organ transplantation, but not significantly (cumulative risk 0.07% *vs.* 0.04% in the control group). At 1-year, there were no reported cases of melanoma which could be due to the relatively short period post-transplantation, not allowing sufficient time for melanoma development or detection. The stabilization of melanoma incidence in the heart Tx group from 5 to 10 years might suggest that the period of highest vulnerability to melanoma in heart transplant recipients was within the first five years following transplantation. The analytical interpretation of this data suggests an epidemiological anomaly where the expected increased risk of melanoma in an immunocompromised cohort, such as heart Tx recipients, was not observed over the long term. Instead, a paradoxical reduction in incidence was noted when compared to the general population.

Our study has several important limitations. Firstly, the detailed data of our interest in the National Health Fund database are only available from 2010 on. Moreover, there is a potential for overdiagnosis (i.e. "overreporting" C43 by general practitioners at referral without proper histopathological diagnosis), which we attempted to mitigate by considering only hospital and clinical data concerning the diagnoses (i.e. we excluded ICD codes entered at primary care units). To further clarify the available dataset, we also compared the obtained number of patients with those in the PolTransplant database. Datasets largely overlap (between 2010 and 2020, 42,756 diagnoses of C43 were established based on National Health Fund data, and respectively, 37,585 based on the National Cancer Registry report [15]). Despite the above, the strength of our report lies in its scrupulous analysis of available data, strict inclusion criteria, and integrating them to create a clinically important consensus.

To the best of our knowledge, the study is the first analysis of such a large population of organ transplant recipients in our country and in Europe, with data sourced from one of the most reliable medical information repositories run by a public governmental agency concerning transplant recipients in Poland.

As the data elucidates, organ transplantation and the associated life-long changes for the patient (like immunosuppression) bring not only benefits, but is also associated with a greater risk of melanoma prevalence, however, it is not as high as previously believed. In our opinion it is obligatory to inform patients and educate them in self-examination techniques, while also encouraging them to undergo frequent follow-up visits for skin lesion control within the first few years post-transplant. Guidelines recommend that transplant recipients should

be screened for skin cancer at least twice a year from five years post-transplantation [16–18]. We hope that the presented results will allow for a real assessment of the risk of developing melanoma in our country, and contribute to standardizing screening practices in this group of patients, offering valuable insights for medical professionals and researchers.

Conclusions

The incidence of melanoma has been observed to increase among renal transplant recipients over the first 10 years post-transplant, with a peak in cases occurring between 4 and 7 years after transplantation. In heart and liver transplant recipients, cases of melanoma are reported within the first 5 years post-transplant, and no new cases have been recorded after this period. The 10-year cumulative melanoma incidence slightly increased in renal recipients (0.213% *vs.* 0.09, $p < 0.001$) and in liver transplant recipients (0.14% *vs.* 0.09%, $p < 0.001$) as opposed to the general population of Poland.

After a thorough analysis of data obtained from the National Health Fund in Poland, our study confirms that melanoma risk increased in the group of renal and liver recipients, but there is no association between melanoma occurrence and heart transplantation. The melanoma risk increase in renal, liver, and heart transplant recipients, although statistically significant, is lower than was believed before the study. The authors particularly emphasize the value of monitoring transplant recipients for skin melanoma, with special attention paid to patients living over 5 years with a transplanted organ.

Article information and declarations

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Ethics statement

No ethical issues or concerns were applicable to this research.

Author contributions

Aleksandra Kulbat – conceptualization, data curation, project administration, resources, software, validation, visualization, writing – original draft preparation, writing – review and editing.

Karolina Richter – visualization, writing – original draft preparation.

Marta Krzysztofik – writing – original draft preparation.

Krzysztof Batko – writing – original draft preparation, formal analysis, validation.

Aleksandra Karwańska – writing – original draft preparation.

Marta Kołodziej-Rzepa – writing – review and editing, supervision.

Tomasz Wojewoda – writing – review and editing, supervision.

Wojciech M. Wysocki – conceptualization, writing – funding acquisition, original draft preparation, writing – review and editing, supervision.

Conflict of interest

None declared

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References

1. Poltransplant Statystyka 2023. http://www.poltransplant.org.pl/statystyka_2023.html#gsc.tab=0 (01.01.2024).
2. Poltransplant Statystyka 2012. http://www.poltransplant.org.pl/statystyka_2012.html (01.01.2024).
3. 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.
4. Lizakowski S, Rutkowski P. Nowotwory u chorych po przeszczepieniu nerki. In: Rutkowski B. ed. Leczenie nerkozastępcze. Wydawnictwo Czelej, Lublin 2007: 409–418.
5. 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.
6. 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.
7. Lesnoni La Parola I, Masini C, Nanni G, et al. Kaposi's sarcoma in renal-transplant recipients: experience at the Catholic University in Rome, 1988-1996. Dermatology. 1997; 194(3): 229–233, doi: 10.1159/000246107, indexed in Pubmed: 9187838.
8. 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.
9. Krajowy Rejestr Nowotworów – Raporty. https://onkologia.org.pl/pl/raporty (01.01.2024).
10. Gandhi SA, Kampp J. Skin Cancer Epidemiology, Detection, and Management. Med Clin North Am. 2015; 99(6): 1323–1335, doi: 10.1016/j.mcna.2015.06.002, indexed in Pubmed: 26476255.
11. Erdei E, Torres SM. A new understanding in the epidemiology of melanoma. Expert Rev Anticancer Ther. 2010; 10(11): 1811–1823, doi: 10.1586/era.10.170, indexed in Pubmed: 21080806.
12. Garrett GL, Blanc PD, Boscardin J, et al. Incidence of and Risk Factors for Skin Cancer in Organ Transplant Recipients in the United States. JAMA Dermatol. 2017; 153(3): 296–303, doi: 10.1001/jamadermatol.2016.4920, indexed in Pubmed: 28097368.
13. Wójcik J, Bułło B, Jassem J, et al. Wtórne nowotwory u biorców przeszczepów nerek – opis czterech przypadków i przegląd piśmiennictwa. Nowotwory. 1998; 48: 751–757.
14. Imko-Walczuk B, Turner R, Wojnarowska F. Malignant melanoma. Cancer Treat Res. 2009; 146: 311–322, doi: 10.1007/978-0-387-78574-5_25, indexed in Pubmed: 19415212.
15. Wójcik J., Bułło B., Jassem J., Zdrojewski Z., Rutkowski B.: Wtórne nowotwory u biorców przeszczepów nerek – opis czterech przypadków.

16. Imko-Walczuk B, Ankudowicz A, Jaśkiewicz J, et al. Skin cancers in patients after organ transplantation. Dermatology Review/Przegląd Dermatologiczny. 2012; 99(2): 97–111.
17. Baker RJ, Mark PB, Patel RK, et al. Renal association clinical practice guideline in post-operative care in the kidney transplant recipient. BMC Nephrol. 2017; 18(1): 174, doi: 10.1186/s12882-017-0553-2, indexed in Pubmed: 28571571.
18. Garrett GL, Blanc PD, Boscardin J, et al. Incidence of and Risk Factors for Skin Cancer in Organ Transplant Recipients in the United States. JAMA Dermatol. 2017; 153(3): 296–303, doi: 10.1001/jamadermatol.2016.4920, indexed in Pubmed: 28097368.
19. SECTION IV: Long-term management of the transplant recipient. Nephrology Dialysis Transplantation. 2002; 17(90004): 3–3, doi: 10.1093/ndt/17.suppl_4.3.

Squamous and basal skin cancers in 17,207 solid organ transplant recipients: Real-world data from national health insurance database in Poland

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Abstract

Background. Immunosuppressive therapy in organ transplant ensures proper graft function for many years, but it is burdened with a negative impact on the development of skin cancer in them.

Objectives. To characterize the impact of immunosuppressive therapy in transplant recipients on the development of non-melanoma skin cancers (NMSC).

Materials and methods. A total of 17,207 Polish patients who underwent liver, heart or kidney transplants between 2010 and 2022 and were on immunosuppression were included in the study. Immunosuppression was most commonly achieved using a regimen of tacrolimus (TAC) or cyclosporine A (CsA) combined with mycophenolic acid (MPA) and glucocorticosteroids (GS). Data on NMSC incidence from the National Health Fund in this population were analyzed and compared against incidence of NMSC in general Polish population in the same period.

Results. Renal transplant recipients demonstrated a significantly elevated risk of NMSC compared to the general population, with a 1-year cumulative incidence of 0.09% vs 0.04% ($p < 0.001$), a 5-year incidence of 1.21% vs 0.18% ($p < 0.001$) and a 10-year incidence of 4.18% vs 0.36% ($p < 0.001$). Liver transplant recipients exhibited an elevated risk for the development of NMSC, which persisted and increased over time (incidence of 0.09% vs 0.04% at 1 year ($p < 0.001$), 0.83% vs 0.18% at 5 years ($p < 0.001$) and 2.65% vs 0.36% at 10 years ($p < 0.001$)). Heart transplant recipients also showed a significantly higher cumulative incidence of NMSC at 1 year (0.09% vs 0.04%, $p < 0.001$), 5 years (0.89% vs 0.18%, $p < 0.001$) and 10 years (4.06% vs. 0.36%, $p < 0.001$) post-transplantation.

Conclusions. Organ transplant recipients have an 2 times at 1 year, 4,5 times after 5 years and 9 times after 10 years increased risk of NMSC on average as opposed to general Polish population in the same period.

Key words: transplantation, skin cancer, transplant recipients, non-melanoma skin cancer

Background

A total of 1,910 organ transplants, including 1,055 kidney transplants, 550 liver transplants and 178 heart transplants, were carried out in Poland in 2023, according to the National Health Fund.[1] This substantially outnumbers earlier figures of transplantation (e.g. 1,608 organ transplants in 2012).[2] Currently, organ transplantations are common worldwide, with the numbers of these procedures performed each year globally reaching hundreds of thousands.

Hailed as the only long-term curative treatment for end-stage liver, heart or kidney disease, organ transplantation involves recipients in extensive, lifelong care. Recipients of the lifelong immunosuppressive therapy required for proper graft function are susceptible to numerous illnesses, and cancer is one of the most common in this group of patients.

Non-melanoma skin cancers (NMSCs), comprising mainly of squamous cell carcinoma (SCC) and basal cell carcinoma (BCC), are the most common tumors developing after organ transplantation and both constitute over 90% of all skin tumors that appear in individuals after organ transplantation.[3]

The outcomes of various studies have receive transplant recipients experience an increased risk of skin malignancy, ranging from 2 to 250 times higher compared to the general population, with the exact risk depending on specific population under investigation.[4–9] The highest increase in this particular risk was observed in Australia (a 250 times higher risk compared to the general population). In this country, the cumulative incidence of skin cancer progressively rises from 7% after 1 year of immunosuppression to 45% after 11 years, eventually reaching 70% after 20 years of immunosuppression.[5] Authors from Scandinavian countries report a 20–100-fold increase in the risk of developing NMSCs.[6,7] In the Netherlands, the risk of skin cancer was observed to be 3% after 5 years, 24% after 15 years and even 40% after 20 years from organ transplantation.[8] In one of the Italian studies, the cumulative risk after 5 years was 7.5%, and after 15 years, it was 28.8%.[9] The risk of developing skin cancer steadily rises in all the presented data as more time passes since the transplantation. However, the numerical values significantly vary among them, even in the European countries sharing similar remaining NMSC risk factors, like long life expectancy, large percentage of elderly in the demographical structure, UV exposure, and cancer awareness within society.[6–9]

Despite sharing a similar geographical latitude, findings from European studies also reveal considerable variation in the risk of neoplasia. This indicates that there may be other risk factors to cancer development, including the effects of administered treatments, genetic predispositions, or the prevalence and influence of HPV infection.[10–13] Regrettably, despite a lot of publications, epidemiological studies with a sizable patient population are lacking; such studies could facilitate an accurate evaluation of the actual risk of skin cancer among transplant recipients in Poland.

Objectives

In this study, we performed a large-scale investigation regarding the specific risk faced by transplant recipients by focusing on the real-world incidence of NMSC in Poland over the last 13 years. The data on skin cancer episodes involving all Polish residents were sourced from the National Health Fund dataset, a governmental public health institution. This is the largest analysis conducted on this topic in Poland to date, aiming to shed light on the frequency and risk factors associated with NMSC among organ transplant recipients.

Materials and methods

The National Health Fund provided information on skin cancer incidence in patients who had received a kidney, heart or liver transplant. The International Classification of Diseases, 10th Revision, Clinical Modification (ICD-10-CM) code for skin cancer (C44.0–C44.9) was used to identify a cohort of patients with a diagnosis of skin cancer based on any inpatient or outpatient claim associated with the dataset. Code C44.0–C44.9 is used by hospitals for reporting to the National Health Fund the diagnosis of NMSC regardless of histopathology (SCC and BCC are reported using the same code). Patients who underwent renal, heart or liver transplantation between 2010 and 2022 are included in the dataset and were identified by specific codes used for transplantation reimbursements by the National Health Fund. A history of prior organ transplantation as well as the transplantation of more than 1 of the specified organs were considered exclusion criteria. Basic demographic characteristics of the patients included in the analysis is presented in the Table 1.

Statistical analyses

The primary objective of this analysis was to compare the cumulative incidence rates of skin malignancies, excluding melanoma, in patients who have undergone organ transplantation (kidney, heart or liver) with those in the general population. An additional aim was to determine whether organ transplantation is a significant risk factor for the development of skin cancers when compared to the general population. The studied hypotheses were formulated as follows:

H_0: The cumulative incidence rate of skin cancer is the same in both the specific post-transplant (Tx) cohort and the general population at each time point (1, 5 and 10 years).

H_1: The cumulative incidence rate of skin cancer differs between the specific Tx cohort and the general population at each time point.

The cumulative incidence rate at specific time point t is calculated as the sum of the incidence rates for each year up to that point using Equation 1:

Table 1. Clinical and demographic characteristics of the solid organ transplants recipients (Tx)

Characteristic	Kindey Tx	Liver Tx	Heart Tx
Mean age at time of organ transplantation [years]	47.97	44.36	46.87
Median age at time of organ transplantation [years]	50.5	50	52
Mean age at the time of NMSC diagnosis [years]	65.36	62.71	62.19
Median age at the time of NMSC diagnosis [years]	68	64	65.75
Mean time to diagnosis [years]	5.02	5.33	6.68
Median time to diagnosis [years]	5.25	5.5	6

NMSC – non-melanoma skin cancer.

$$Cumulative\ incidence\ rate = \sum_{i=0}^{t} \frac{New\ events_i}{At\ risk_i} \quad (1)$$

We compared cumulative incidence rates of skin cancer between the Tx cohort and the general population at 1 year, 5 years and 10 years using a Z-test for 2 proportions.

The proportion of patients who developed skin cancer by the specified time point (1, 5 or 10 years) was calculated for both the Tx cohort and the general population.

The pooled incidence rate was calculated with Equation 2:

$$\hat{p} = \frac{n_{Tx} \cdot \hat{p}_{Tx} + n_{Pop} \cdot \hat{p}_{Pop}}{n_{Tx} + n_{Pop}} \quad (2)$$

where n_{Txn} and n_{Pop} represent the number of patients at risk in the Tx cohort and general population, respectively; $\hat{P}_{Tx}$– cumulative incidence rate in the Tx cohort; and $\hat{P}_{Pop}$– cumulative incidence rate in general population.

The Z-statistic for comparing the cumulative incidence rates between the cohort of patients after transplantation and overall population was calculated using Equation 3:

$$Z = \frac{\hat{p}_{Tx} - \hat{p}_{Pop}}{\sqrt{\hat{p}\left(1-\hat{p}\right) \cdot \left(\frac{1}{n_{Tx}} + \frac{1}{n_{Pop}}\right)}} \quad (3)$$

This Z-statistic was compared to the standard normal distribution to obtain the p-value.

When comparing the Tx cohort to the general population, the Tx cohort is not excluded from the population dataset. Due to the very small proportion of Tx patients, their inclusion does not impact the observed differences.

An alpha level $\alpha = 0.05$ was set as the criterion for determining statistical significance. A $p < 0.05$ was considered statistically significant, indicating a difference in cumulative incidence rates between the 2 groups at the respective follow-up periods.

Moreover, to establish a transplantation as a risk factor, we estimated risk ratio (RR) comparing the risk of skin cancer in the transplantation cohort to the risk in the general population using Equation 4:

$$RR = \frac{Incidence\ rate\ in\ Tx\ cohort}{Incidence\ rate\ in\ General\ population} \quad (4)$$

To compute the 95% confidence interval (95% CI) for RR, we applied an approximation for the standard error (SE) of the logarithm of the RR using Equation 5:

$$SE_{logRR} = \sqrt{\frac{1}{e_{Tx}} + \frac{1}{e_{Pop}}} \quad (5)$$

where e_{Tx}, e_{Po} is the number of skin cancer events in the Tx cohort and overall population respectively.

The 95% CI for RR was calculated using Equations 6,7.

$$CI_{lower} = e^{log(RR) - 1.96 \times SE_{logRR}} \quad (6)$$

$$CI_{upper} = e^{log(RR) + 1.96 \times SE_{logRR}} \quad (7)$$

The RR is significantly greater than 1.0, which suggested that the transplantation is a risk factor for skin cancer.

Analyses were conducted using the R statistical language (v. 4.3.3; R Core Team, 2024; R Foundation for Statistical Computing, Vienna, Austria) on Windows 11 Pro 64 (build 22631).

We computed the cumulative incidence rate of NMSC, coded as C44, among recipients of organ transplants (Tx) in comparison to a control group over a 1-, 5- and 10-year follow-up period.

The Polish National Cancer Registry provided the information used to build the dataset for this time period (2010–2022).[14]

Results

Population of patients with non-melanoma skin cancer (C44)

The population of Poland during the period from 2013 to 2022, according to data from the World Bank,[15] ranged from 38.04 million at the beginning of the analyzed timeframe to 36.1 million by the final year of assessment. Incidence data for the respective years within the study period were derived based on the findings of the reports from the Polish National Cancer Registry.[16] The search criteria were focused on identifying newly reported cases of incidence associated with NMSC (C44) across the entirety of the Polish region, encompassing both genders and all age groups.

The cumulative incidence rates were calculated in accordance with established epidemiological methodologies, taking into account the annual variations in population size as well as the yearly incidence of new cancer cases reported by the Polish National Cancer Registry. These results, as detailed in Table 2, provide insight into the burden of skin cancer in the Polish population over a 10-year

Table 2. Risk table of non-melanoma skin cancer (NMSC) events (C44) with follow-up over 10 years (2013–2022) in patients' Polish population

Year	Follow-up [years]	Patients at risk	NMSC (C44)	
			new events	cumulative incidence rate [%]
2013	1	38,040,196	13,516	0.0355
2014	2	38,011,735	14,470	0.0736
2015	3	37,986,412	13,267	0.1085
2016	4	37,970,087	12,506	0.1413
2017	5	37,974,826	13,731	0.1774
2018	6	37,974,750	14,502	0.2155
2019	7	37,965,475	14,687	0.2542
2020	8	37,899,070	10,810	0.2826
2021	9	37,747,124	13,633	0.3185
2022	10	36,821,749	15,716	0.3597

Table 3. Risk table of non-melanoma skin cancer (NMSC) events (C44) with follow-up over 10 years in patients after kidney transplantation

Follow-up [years]	Patients at risk	NMSC (C44)	
		new events	cumulative incidence rate [%]
0	12,205	0	0.0000
1	11,673	10	0.0857
2	10,676	19	0.2636
3	9,788	24	0.5088
4	8,895	30	0.8461
5	7,870	29	1.2145
6	6,893	35	1.7227
7	5,868	28	2.1993
8	4,859	27	2.7550
9	3,920	22	3.3162
10	2,998	26	4.1835

follow-up period. The results demonstrate a steady increase in the cumulative incidence rates for NMSC (C44) over the 10-year follow-up period in the Polish population.

The incidence of NMSC (C44) is significantly higher from the outset, with a cumulative incidence rate starting at 0.0355% in 2013 and increasing to 0.3597% by 2022. The consistently higher annual incidence, ranging from 10,810 to 15,716 cases, suggests that NMSC represent a more substantial and increasing risk to the population.

Cohort of patients with kidney transplantation

The number of patients at risk for developing skin malignancies following kidney transplantation, over the period from 2010 to 2022, was approx. 12,205, as detailed in Supplementary Table 1. This cohort represents individuals who underwent kidney transplantation and were subsequently exposed to long-term immunosuppressive therapy, which is well-documented to increase the risk of certain malignancies, particularly skin cancers.[5–9]

Table 3 provides a detailed summary of the cumulative incidence of non-melanoma skin cancer (NMCS) (C44) over a 10-year follow-up period post-transplantation.

Notably, the cumulative incidence rate for other skin malignancies is significantly higher, rising from 0.0857% at 1 year to 4.1835% after 10 years.

Results of comparing incidents rate between the cohort of patients after kidney transplantation and overall population are reported in Table 4.

The results in Table 4 indicate that kidney transplant recipients have a significantly higher risk of developing NMSC (C44) compared to the general population. The risk ratio for NMSC (C44) at 1 year, the cumulative incidence rate for transplant recipients is 0.0857%, with an RR = 2.41, indicating more than double the risk compared to the general population. By 5 years, the incidence rate rises dramatically to 1.2145%, with an RR = 6.84, and by 10 years it reaches 4.1835%, with an RR = 11.63. These findings demonstrate that kidney transplant recipients are at a significantly elevated risk of developing NMSC over time, with the risk increasing substantially as the follow-up period lengthens.

Table 4. Results of Z-test and RR for cumulative incidence of NMSC (C44) in kidney transplant recipients compared to the general population

Event	FU	Cumulative incidence rate [%]		z	p-value	RR	95% CI
		Tx	population				
NMSC (C44)	1Y	0.0857	0.0355	29.30	<0.001	2.41	1.29–4.48
	5Y	1.2145	0.1774	240.71	<0.001	6.84	5.69–8.24
	10Y	4.1835	0.3597	436.16	<0.001	11.63	10.27–13.17

RR – risk ratio; 95% CI – 95% confidence interval.

The Z-test results for NMSC is highly significant ($p < 0.001$) at all time points, showing that the observed differences between the transplant cohort and the general population are not due to random chance. This strongly supports the conclusion that organ transplantation, specifically kidney transplantation, is a major risk factor for the development of NMSC.

Liver transplant recipients vs general population

The data from Table 5 indicate that patients who undergo liver transplantation are at an elevated risk for NMSC (C44) over a 10-year period. By the end of the first year, 3 new cases of NMSC are observed, resulting in a cumulative incidence rate of 0.0931%. This rate continues to rise. By year 5, the cumulative incidence of NMSC reaches 0.8311%, and by year 10, it escalates to 2.6462%. The consistent appearance of new cases throughout the follow-up period, especially between years 5 and 10, highlights the prolonged and progressive risk of NMSC in liver transplant recipients.

The results from Table 6 show that liver transplant recipients are at a significantly higher risk of developing NMSC (C44) compared to the general population. The risk for other skin malignancies (C44) is pronounced. At 1 year, the cumulative incidence rate in liver transplant recipients is 0.0931%, with an RR = 2.61 (95% CI: 0.84–8.12), suggesting a moderately increased risk, though with some uncertainty due to the wide confidence interval. By 5 years, the cumulative incidence rises sharply to 0.8311%, with an RR = 4.68 (95% CI: 2.99–7.35), reflecting a significantly elevated and more precisely estimated risk. At 10 years, the cumulative incidence for NMSC reaches 2.6462%, with an RR = 7.35 (95% CI: 6.77–7.99), indicating that

Table 5. Risk table of non-melanoma skin cancer (NMSC) events (C44) with follow-up over 10 years in patients after liver transplantation

Follow-up [years]	Patients at risk	NMSC (C44)	
		new events	cumulative incidence rate [%]
0	3,584	0	0.0000
1	3,224	3	0.0931
2	2,819	3	0.1995
3	2,499	4	0.3595
4	2,200	1	0.4050
5	1,878	8	0.8311
6	1,609	2	0.9555
7	1,316	5	1.3355
8	1,059	0	1.3355
9	777	6	2.1076
10	557	3	2.6462

Table 6. Results of Z-test and RR for cumulative incidence of non-melanoma skin-cancers (NMSC)in liver transplant recipients compared to the general population

Event	FU	Cumulative incidence rate [%]		z	p-value	RR	95% CI
		Tx	population				
NMSC (C44)	1Y	0.0931	0.0355	17.67	<0.001	2.61	0.84–8.12
	5Y	0.8311	0.1774	74.15	<0.001	4.68	2.99–7.35
	10Y	2.6462	0.3597	112.44	<0.001	7.35	6.77–7.99

RR – risk ratio; 95% CI – 95% confidence interval.

liver transplant recipients are more than 7 times as likely to develop NMSC compared to the general population. This long-term risk is highly significant and consistent.

The Z-test results are significant ($p < 0.001$) for NMSC at all time points, confirming that the differences in cumulative incidence rates between liver transplant recipients and the general population are statistically significant. The data clearly established liver transplantation as a major risk factor for NMSC, where the risk increases markedly over time.

These findings highlight the critical need for regular dermatologic screening and preventive strategies in liver transplant recipients, with a specific focus on NMSC, which pose a substantial and growing risk in this population.

Heart transplant (Tx) recipients vs general population

The following Table 7 presents the risk of developing NMSC over a 10-year period in a cohort of heart transplant recipients. The data highlight both the cumulative incidence of these cancers and the number of new events at each follow-up interval, providing valuable insights into the timing and progression of skin cancer risk in this vulnerable population.

The data in Table 7 highlight the increasing cumulative incidence of non-melanoma skin cancer (NMSC) (C44) over a 10-year follow-up period in heart transplant recipients. The incidence of NMSC (C44) shows a steady increase over time, with new events occurring consistently throughout the follow-up period. By the 10th year, the cumulative incidence rate of NMSC reaches 4.0609%, indicating a high risk. The data suggest that heart transplant recipients are at significantly greater risk for NMSC, with the risk progressively increasing as follow-up extends.

The data in Table 8 show a distinct pattern of non-melanoma skin cancer (NMSC) risk in heart transplant recipients compared to the general population. The risk of NMSC (C44) is high and clearly defined. At 1 year, the cumulative incidence rate in heart transplant recipients is 0.0909%, with an RR = 2.56 compared to the general population. Although this indicates more than double the risk, the confidence interval (95% CI: 0.37–18.18) suggests a lack of precision, likely due to the smaller number of cases early on. By 5 years, the cumulative incidence rate increases sharply to 0.8871%, with an RR = 5.00 and a much narrower confidence interval (95% CI: 2.24–11.13), demonstrating a significantly elevated risk. At 10 years, the cumulative incidence reaches 4.0609%, with an RR = 11.29, and the confidence interval (95% CI: 9.64–13.22) indicates a highly significant and reliable increase in the risk of NMSC in heart transplant recipients.

The Z-test results across all time points for NMSC is significant ($p < 0.001$), confirming that the differences in cumulative incidence rates between heart transplant recipients and the general population are not due to chance.

Table 7. Risk table of NMSC events (C44) with follow-up over 10 years in patients after heart transplantation

Follow-up [years]	Patients at risk	NMSC (C44)	
		new events	cumulative incidence rate [%]
0	1,418	0	0.0000
1	1,099	1	0.0909
2	918	1	0.1998
3	740	1	0.3349
4	616	1	0.4972
5	513	2	0.8871
6	418	1	1.1263
7	341	1	1.4195
8	276	1	1.7818
9	204	2	2.7622
10	154	2	4.0609

Table 8. Results of Z-test and RR for cumulative incidence of NMSC (C44) in heart transplant recipients compared to the general population

Event	FU	Cumulative incidence rate [%]		z	p-value	RR	95% CI
		Tx	population				
Other skin malignancies (C44)	1Y	0.0909	0.0355	9.92	<0.001	2.56	0.37–18.18
	5Y	0.8871	0.1774	42.08	<0.001	5.00	2.24–11.13
	10Y	4.0609	0.3597	95.71	<0.001	11.29	9.64–13.22

RR – risk ratio; 95% CI – 95% confidence interval.

Discussion

Following organ donation, NMSC are frequent and significantly increase mortality.[13,17] Numerous research studies have looked at the risk of NMSC following transplantation, showing a wide range of the reported rise in incidence. This raises many questions regarding the scale of this phenomenon in Poland. The studies that are available so far for the Polish population either focus on a small number of participants, describe individual cases, or relate to earlier periods when immunosuppressive medication was frequently administered differently than it is today.[16–19] The purpose of our research was to reexamine the relationship between Poland's organ transplant recipients and the incidence of SCC or BCC in comparison with the corresponding incidence observed over the same time span across the general Polish population. After analyzing data from the National Health Fund, we discovered that abundant NMSC cases were present in the 3 most numerous post-transplant patient groups: those who had received a kidney, liver or heart transplant.

Upon comparing data from the National Health Found to population data published by the National Cancer Registry,[14] the risk of NMSC occurrence in renal transplant recipients was nearly 12 times higher after 10 years of transplantation compared to the population risk at the same time (cumulative risk 4.18% vs 0.36%). The escalating incidence in the renal transplant recipient cohort over time is probably indicative of a persistent and compounding risk factor for NMSC attributable to long-term immunosuppressive treatment, which may not only enhance the survival of malignant cells but also promote the accumulation of oncogenic mutations and inhibit the body's natural antitumor immune defenses. This impact of immunosuppression seems to be independent from other well-known risk factors, like UV exposure, as other risk factors are evenly affecting general population in Poland as equally as they affect post-transplant patients.

The 10-year data also show an increase in the cumulative risk to 2.65% among liver transplant patients, compared to 0.36% in the general population (2010–2022). This enduring elevation in NMSC incidence underscores the chronic risk associated with long-term immunosuppression and possible additional hepatic comorbidities that may further compromise immune surveillance against skin cancer.

Patients who have undergone heart transplants in Poland also statistically more frequently received a NMSC diagnosis over the course of follow-up. Cumulative incidence climbs to 4.06%, compared to 0.36% within the general population during the same time. This trend suggests a continued increased risk of NMSC associated with long-term immunosuppression, and possibly other factors unique to heart transplant recipients, such as the increased incidence of viral infections that can contribute to skin cancer risk. In conclusion, the cumulative risk of NMSC compared to the general population is also significantly higher in all 3 mentioned groups of patients.

Limitations

It should be noted that our investigation is subject to various limitations. Firstly, information from the National Health Fund database on the matter is limited to the period after 2010. Furthermore, we tried to reduce the possibility of overdiagnosis by only taking into account hospital and clinical data related to the diagnoses (i.e., we eliminated ICD codes entered into the national online reporting system at primary care facilities without prior histopathological confirmation). Additionally, since SCC and BCC were not given distinct ICD-10 codes, it is not possible to conduct a separate analyses on the incidence of these 2 skin malignancies. Fortunately, since 2022, all Polish pathology reports have been entered into nationwide online reporting system, which in future will enable pathology diagnosis-directed, rather than code-based, analysis.

Additionally, another weakness of this study is the well-known phenomenon of underreporting of skin cancers like SCC and BCC.[20] On the other hand, the underreporting of the C44 code applies to the same extent both to transplant recipients and the general population, thus allowing for valid comparison.

There are many well-established factors influencing the increased incidence of skin cancers, such as the patient's age, UV exposure or HPV infection. However exposure to these factors is no different in general population and its subpopulation of transplant recipients in Poland. It might be even speculated, that transplant recipients are younger as opposed to general population at the time of NMSC diagnosis – we are currently exploring that issue in the ongoing further epidemiological study. Therefore, we believe that they do not have a significant impact on the final result.

Additionally, the type of immunosuppression used and the duration of its application also affect the incidence of cancers. There are many drugs and their combinations used in organ recipients to prevent the rejection of the transplanted organ. However the most commonly used immunosuppressive treatment regimen for solid organ transplant recipients in our dataset was: tacrolimus (TAC) or cyclosporine A (CsA) combined with mycophenolic acid (MPA) and glucocorticosteroids (GS). We are intending to perform subgroups analyses on strictly and narrowly defined groups receiving specific immunosuppression.

Nevertheless, the strength of the report derives from a rigorous examination of the available data, stringent inclusion criteria, and their integration to produce a clinically meaningful consensus. Utilizing data from one of the most trustworthy medical information repositories for transplant recipients in Poland, this study represents, to the best of our knowledge, the first extensive analysis of such a large group of organ transplant recipients in Poland and presumably in Europe as well. According to our research, organ transplantation and subsequent immunosuppression exposes transplant recipients to a much

higher risk of NMSC. This underlines the need to comprehensibly inform the patients on the risk and educate them how to perform self-examinations.[21] It was acknowledged in recently published Polish Oncological Society guidelines for melanoma and NMSC post-treatment surveillance – 5 years following transplantation, guidelines advise that patients who have undergone transplantation should have their skin evaluated for cancer at least twice a year.[22–24]

Conclusions

The risk of NMSC in patients who have long-term survived renal, heart and liver transplants has been steadily rising over time since transplantation in Poland. Based on >17,000 transplant recipients, we concluded that the risk of developing NMSC after transplantation was higher than the general population risk. The 10-year cumulative incidence of NMSC increased in renal (4.18% vs 0.36, $p < 0.001$), liver (2.65% vs 0.36, $p < 0.001$) and heart recipients (4.06% vs 0.36, $p < 0.001$) vs general Polish population. The overall NMSC risk was continuously rising since transplantation staring from on average 2 times higher risk at 1 year to 12 times higher risk after 10 years compared to the risk of NMSC in general Polish population.

Supplementary data

The Supplementary materials are available at https://doi.org/10.5281/zenodo.14606095. The package includes the following files:

Patient population at risk following kidney, heart, and liver transplantation in 2010–2022.

Supplementary Table 1. Number of patients at risk following kidney transplantation by year of transplantation with 10-year follow-up.

Supplementary Table 2. Number of patients at risk following heart transplantation by year of transplantation with 10-year follow-up.

Supplementary Table 3. Number of patients at risk following liver transplantation by year of transplantation with 10-year follow-up.

Data availability

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Consent for publication

Not applicable.

Use of AI and AI-assisted technologies

Not applicable.

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References

1. Poltransplant. Statystyki 2023. 2023. https://poltransplant.org.pl/statystyka-2024/statystyka-2023. Accessed January 27, 2024.
2. Poltransplant. Biuletyn Informacyjny Poltransplant 1(21) 2013. Warsaw, Poland: Poltransplant; 2013. https://poltransplant.org.pl/wp-content/uploads/2024/08/Biuletyn_2013.pdf. Accessed January 27, 2025.
3. 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
4. Wisgerhof HC, Wolterbeek R, de Fijter JW, Willemze R, Bouwes Bavinck JN. Kidney transplant recipients with cutaneous squamous cell carcinoma have an increased risk of internal malignancy. *J Invest Dermatol*. 2012;132(9):2176–2183. doi:10.1038/jid.2012.132
5. Bouwes Bavinck JN, Hardie DR, Green A, et al. The risk of skin cancer in renal transplant recipients in Queensland, Australia: A follow-up study. *Transplantation*. 1996;61(5):715–721. doi:10.1097/00007890-199603150-00008
6. 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
7. Naldi L, Fortina AB, Lovati S, et al. Risk of nonmelanoma skin cancer in Italian organ transplant recipients: A registry-based study. *Transplantation*. 2000;70(10):1479–1484. doi:10.1097/00007890-200011270-00015
8. Lesnoni La Parola I, Masini C, Nanni G, Diociaiuti A, Panocchia N, Cerimele D. Kaposi's sarcoma in renal-transplant recipients: Experience at the Catholic University in Rome, 1988–1996. *Dermatology*. 1997;194(3):229–233. doi:10.1159/000246107
9. 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
10. Gandhi SA, Kampp J. Skin cancer epidemiology, detection, and management. *Med Clin North Am*. 2015;99(6):1323–1335. doi:10.1016/j.mcna.2015.06.002
11. American Cancer Society (ACS). Basal and squamous cell skin cancer risk factors. 2009. www.cancer.org/cancer/types/basal-and-squamous-cell-skin-cancer/causes-risks-prevention/risk-factors.html. Accessed August 15, 2024.
12. Erdei E, Torres SM. A new understanding in the epidemiology of melanoma. *Exp Rev Anticancer Ther*. 2010;10(11):1811–1823. doi:10.1586/era.10.170
13. Garrett GL, Blanc PD, Boscardin J, et al. Incidence of and risk factors for skin cancer in organ transplant recipients in the United States. *JAMA Dermatol*. 2017;153(3):296–303. doi:10.1001/jamadermatol.2016.4920
14. Imko-Walczuk B, Ankudowicz A, Jaśkiewicz J, Lizakowski S, Dębska-Ślizień A, Rutkowski B. Skin cancers in patients after organ transplantation [in Polish]. *Przegl Dermatol*. 2012;99(2):97–111. https://www.termedia.pl/Raki-skory-u-chorych-po-przeszczepieniu-narzadow,56,18517,1,0.html. Accessed August 25, 2024.
15. World Bank Group. Population Total. 2024. https://data.worldbank.org/indicator/SP.POP.TOTL?locations=PL. Accessed November 20, 2024.
16. Polish National Cancer Registry. *Raporty*. Warsaw, Poland: Polish National Cancer Registry; 2024. https://onkologia.org.pl/pl/raporty. Accessed November 20, 2024.
17. Lizakowski S, Imko-Walczuk B, Dębska-Ślizień A, Rutkowski B. Nowotwory u chorych po przeszczepieniu nerki. *Forum Nefrol*. 2011;4(3):214–223. https://journals.viamedica.pl/renal_disease_and_transplant/article/view/18525. Accessed August 25, 2024.
18. Imko-Walczuk B, Turner R, Wojnarowska F. Malignant melanoma. *Cancer Treat Res*. 2009;146:311–322. doi:10.1007/978-0-387-78574-5_25
19. Kulbat A, Wysocki WM. Multiple non-melanoma skin cancers during 43-years long therapy with azathioprine in renal transplant recipient. *Nowotwory J Oncol*. 2024;74(4):286. doi:10.5603/njo.100154

20. Gruber P, Zito PM. Skin cancer. In: *StatPearls*. Treasure Island, USA: StatPearls Publishing; 2024:Bookshelf ID: NBK441949. http://www.ncbi.nlm.nih.gov/books/NBK441949. Accessed January 2, 2025.
21. Kulbat A, Richter K, Krzysztofik M, et al. Melanoma incidence in 17,252 organ transplant recipients in Poland in 2010–2022. *Nowotwory J Oncol*. 2024;74(3):173–179. doi:10.5603/njo.99186
22. Wysocki WM, 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 J Oncol*. 2024;74(3):197–202. doi:10.5603/njo.99894
23. Baker RJ, Mark PB, Patel RK, Stevens KK, Palmer N. Renal association clinical practice guideline in post-operative care in the kidney transplant recipient. *BMC Nephrol*. 2017;18(1):174. doi:10.1186/s12882-017-0553-2
24. EBPG Expert Group on Renal Transplantation. European best practice guidelines for renal transplantation. Section IV: Long-term management of the transplant recipient. *Nephrol Dial Transplant*. 2002; 17(Suppl 4):1–67. PMID:12484407.

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Multiple non-melanoma skin cancers during 43-years long therapy with azathioprine in renal transplant recipient

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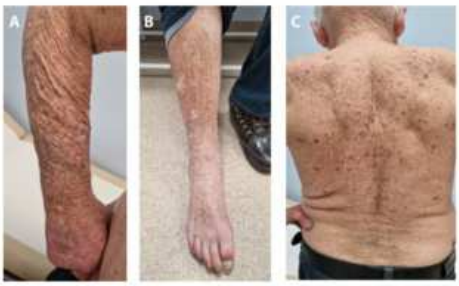

Figure 1A–C. A 75-year-old patient presented with numerous skin lesions on the limbs and trunk morphologically consistent with SCC and BCC

Non-melanoma skin cancers (NMSC), mainly squamous cell carcinoma (SCC) and basal cell carcinoma (BCC), account for over 90% of all skin cancers in solid organ transplant recipients. NMSC incidence steadily increases over time following transplantation, mainly due to exposure to long-term immunosuppression and additional factors such as ultraviolet radiation, ionizing radiation and human papillomavirus (HPV) infection [1–2]. A 75-year-old patient presented with numerous skin lesions on the limbs and trunk morphologically consistent with SCC and BCC (Fig. 1A–C). In the 1970s he was diagnosed with end-stage renal failure, likely due to chronic glomerulonephritis. After months of dialysis, a kidney transplant from a deceased donor was performed in 1980. Since the transplantation he has been on continuous immunosuppressive therapy (azathioprine 50 mg once daily and prednisone 5 mg once daily). This regime is currently known to have strong carcinogenic effects with long-term use [3]. The most suspicious skin lesions on his right thigh, left arm, and left submandibular area were removed with a few millimeters margins and were histologically confirmed as SCC *in situ* (right thigh) and BCC (left arm and left submandibular area). Apart from these three lesions, patient had multiple SCCs and BCCs removed over past decades. Ongoing immunosuppression, coupled with the current condition of his skin (Fig. 1A–C), suggests that new foci of NMSC are expected to develop in the near future. This case clearly emphasizes the urgent need for strict and systematic skin monitoring of organ transplant recipients on long-term immunosuppressive therapy, considering the increased risk of developing NMSC. Awareness of this risk, along with early detection and intervention, significantly improves the general prognosis and quality of life for these patients.

References

1. Basal and Squamous Cell Skin Cancer Risk Factors. American Cancer Society. 2009. www.cancer.org/cancer/types/basal-and-squamous-cell-skin-cancer/causes-risks-prevention/risk-factors.html (03.2024).
2. 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.
3. Kauffman HM, Cherikh WS, McBride MA, et al. Post-transplant de novo malignancies in renal transplant recipients: the past and present. Transpl Int. 2006; 19(8): 607–620, doi: 10.1111/j.1432-2277.2006.00330.x, indexed in Pubmed: 16827677.

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5. Zbiorcze omówienie wyników i podsumowanie cyklu

Pierwszy artykuł wchodzący w skład cyklu stanowiącego rozprawę doktorską to przegląd systematyczny i metaanaliza dostępnego piśmiennictwa naukowego, dotyczącego wpływu zastosowania CNI na ryzyko wystąpienia nowotworów skóry u biorców nerki. Artykuł ten odpowiada pierwszemu celowi szczegółowemu, wskazanemu w rozdziale 3. Wybór tej grupy pacjentów jest podyktowany faktem, iż nerka jest najczęściej przeszczepianym narządem litym w Polsce i na świecie [1, 2], natomiast CNI stanowią jeden z głównych elementów schematów immunosupresyjnych stosowanych w okresie po przeszczepieniu. Zastosowanie tych leków umożliwia roczne przeżycie przeszczepu u 90–95% biorców i ogranicza ryzyko ostrego odrzutu narządu do niespełna 20% [21]. W celu wyszukania odpowiednich danych przeszukano trzy międzynarodowe, elektroniczne bazy danych bibliograficznych: PubMed, Scopus oraz Web of Science. Włączone artykuły obejmowały dane dotyczące biorców nerki z Europy, Azji, Australii i USA, u których wykonano przeszczepienie nerki w latach 1966–2016. Ostatecznie do analizy zbiorczej zakwalifikowano 7 publikacji, obejmujących badania kliniczne z randomizacją, badania kohortowe i badania kliniczno-kontrolne.

Analizę danych przeprowadzono w trzech podgrupach, aby ocenić i porównać ryzyko wystąpienia CM, NMSC oraz całkowite ryzyko wystąpienia nowotworu skóry u biorców nerki. W grupie 270 962 pacjentów stosujących CNI, których dane włączono do metaanalizy, powyższe ryzyko zostało porównane z ryzykiem charakteryzującym 38 313 pacjentów stosujących wyłącznie leki immunosupresyjne należące do innych grup. Następnie obliczono, dla każdej z grup, wskaźnik określający liczbę pacjentów, którzy muszą zostać poddani leczeniu z użyciem CNI, aby u jednej z nich wystąpiło końcowe działanie niepożądane w postaci wystąpienia danego nowotworu skóry (ang. *number needed to harm* – NNH).

Przeprowadzona metaanaliza wykazała statystycznie istotny związek pomiędzy stosowaniem CNI a zwiększonym, w porównaniu z grupą pacjentów stosującą inne niż CNI leki, ryzykiem wystąpienia CM u biorców przeszczepu nerki (iloraz szans [*odds ratio* – OR] 1,09; $p < 0,01$), z NNH wynoszącą 1541,1. Ryzyko wystąpienia NMSC w grupie pacjentów leczonych CNI również było wyższe niż w grupie stosującej schematy immunosupresji zawierające wyłącznie leki należące do innych grup (OR 1,16; $p < 0,01$), a NNH wyniosła 330,7. Analiza całkowitego ryzyka wystąpienia nowotworu skóry (tj. CM i NMSC łącznie) u biorców nerki wykazała, że dla chorych stosujących CNI ryzyko wystąpienia zdarzenia końcowego było wyższe w porównaniu z pacjentami przyjmującymi leki inne niż CNI (OR 1,28; $p < 0,01$), a NNH wyniosła 567,8. Wyniki przeprowadzonej metaanalizy wskazują, że u pacjentów po przeszczepieniu nerki, którzy są długoterminowo leczeni CNI, ryzyko wystąpienia zarówno CM, jak i NMSC jest wyższe w porównaniu z pacjentami stosującymi wyłącznie leki immunosupresyjne należące do innych grup.

Drugi artykuł cyklu to analiza epidemiologiczna surowych krajowych danych pozyskanych z NFZ oraz KRN, dotycząca ryzyka występowania CM w grupie pacjentów po przeszczepieniu nerki, wątroby lub serca wykonanym w latach 2010–2022. W grupie 17 252 biorców, którzy otrzymali jeden z tych trzech narządów litych, zidentyfikowano przypadki występowania CM na podstawie kodów ICD-10 (C43.0–C43.9). Aby uniknąć nadsprawozdawczości postanowiliśmy, tak jak w artykule trzecim (przedstawionym dalej), wyłączyć z analizy rozpoznania CM ustalone w trybie ambulatoryjnym, które zwykle są stawiane jedynie na podstawie obrazu klinicznego, bez potwierdzenia w badaniu histopatologicznym. Następnie przeprowadzono porównanie ryzyka kumulacyjnego wystąpienia CM u biorców narządów po 1-, 5- i 10-letnim okresie obserwacji z ryzykiem populacyjnym wystąpienia CM w tym samym okresie, które obliczono na podstawie danych udostępnionych przez KRN. Sposób prezentacji uzyskanych wyników w tym omówieniu został

ujednolicony z metodą zastosowaną w artykule trzecim niniejszej rozprawy, aby ułatwić ich zestawienie z wynikami dotyczącymi NMSC. Poczynione w tym celu nieznaczne modyfikacje metodyki statystycznej wyjaśniają niewielkie różnice w wynikach prezentowanych w poszczególnych artykułach oraz w niniejszym omówieniu. Różnice te nie wpływają jednak znacząco na wyniki końcowe.

Analiza wykazała, że w grupie 12 205 biorców nerek, po rocznym okresie obserwacji, określono ryzyko występowania CM jako 0,017%, co było istotnie wyższą wartością niż w populacji ogólnej, w przypadku której ryzyko wystąpienia CM w tym samym okresie wynosiło 0,008%. Po 5 i 10 latach ryzyko kumulacyjne wystąpienia CM w grupie biorców w porównaniu z populacją ogólną wynosiło odpowiednio 0,167% *vs* 0,047% oraz 0,358% *vs* 0,098%. Wszystkie prezentowane wyniki były istotne statystycznie dla każdego z porównań ($p < 0,001$) (tab. 1).

Tabela 1. Wyniki testu Z i RR dla skumulowanej zapadalności na CM (C43) u biorców nerki w porównaniu z zapadalnością w populacji ogólnej.

	Okres obserwacji	Ryzyko kumulacyjne (%)		z	wartość p	RR	95% CI
		biorcy	populacja				
CM (C43)	1 rok	0,0171	0,0083	10,48	<0,001	2,06	0,51–8,23
	5 lat	0,1667	0,0472	49,97	<0,001	3,53	2,16–5,77
	10 lat	0,3578	0,0981	47,80	<0,001	3,64	2,48–5,36

W grupie 3584 biorców wątroby, różnica ryzyka kumulacyjnego wystąpienia czerniaka skóry w porównaniu z ryzykiem populacyjnym również była istotna statystycznie w każdym z okresów obserwacji. Po roku skumulowana zachorowalność na CM w grupie biorców wynosiła 0,031%, a w populacji Polski 0,008% ($p < 0,001$). Po 5 latach od przeszczepienia zapadalność wśród biorców wątroby wynosiła 0,204% *vs* 0,047% w populacji ogólnej

(p < 0,001). Po 10 latach obserwacji ryzyko kumulacyjne wystąpienia CM u biorców wątroby wynosiło natomiast 0,204%, podczas gdy w populacji ogólnej osiągnęło 0,098% (p < 0,001) (tab. 2).

Tabela 2. Wyniki testu Z i RR dla skumulowanej zapadalności na CM (C43) u biorców wątroby w porównaniu z zapadalnością w populacji ogólnej.

	Okres obserwacji	Ryzyko kumulacyjne (%)		z	wartość p	RR	95% CI
		biorcy	populacja				
CM (C43)	1 rok	0,0310	0,0083	14,20	<0,001	3,72	0,52–26,45
	5 lat	0,2043	0,0472	32,10	<0,001	4,32	1,80–10,40
	10 lat	0,2043	0,0981	8,42	<0,001	2,08	0,87–5,00

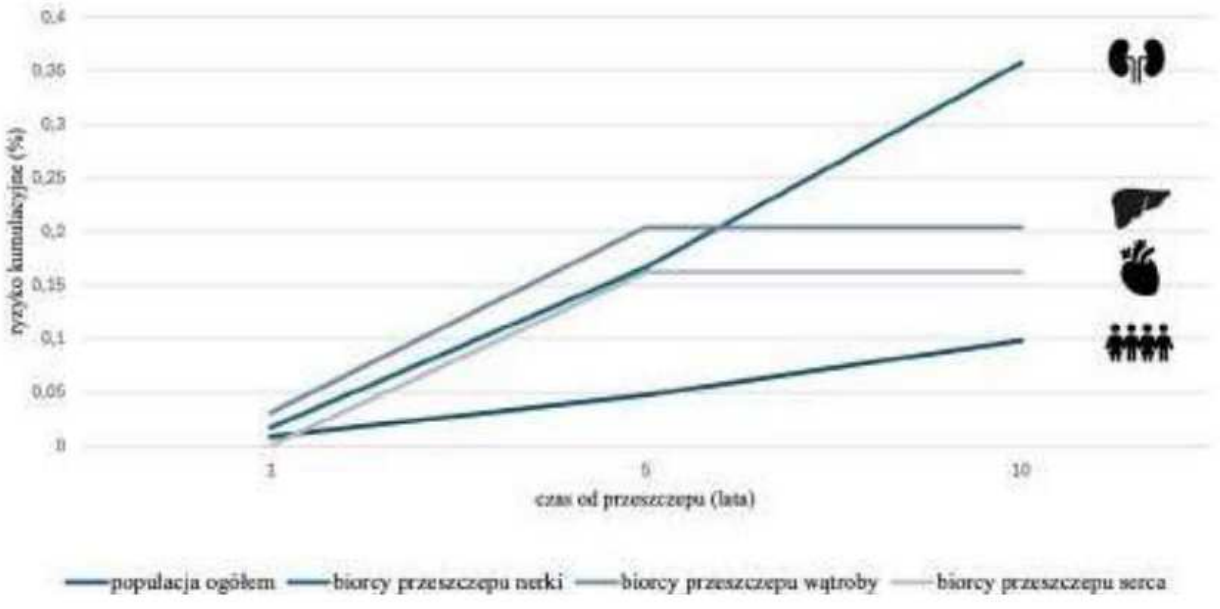
W grupie 1408 biorców serca, po pierwszym roku obserwacji nie odnotowano przypadków CM. Po 5 latach natomiast stwierdzono CM u 0,162% biorców, co było statystycznie istotnie wyższą wartością w porównaniu z wartością ryzyka populacyjnego, które za ten okres wyniosło 0,047% (p < 0,001). Po 10 latach ryzyko kumulacyjne CM w grupie biorców wynosiło 0,162% i również było znamiennie wyższe (p = 0,001) w porównaniu z ryzykiem w populacji ogólnej, które w tym samym przedziale czasowym osiągnęło 0,098% (tab. 3).

Tabela 3. Wyniki testu Z i RR dla skumulowanej zapadalności na CM (C43) u biorców serca w porównaniu z zapadalnością w populacji ogólnej.

	Okres obserwacji	Ryzyko kumulacyjne (%)		z	wartość p	RR	95% CI
		biorcy	populacja				
CM (C43)	1 rok	0,0000	0,0083	–3,03	0,002	–	–
	5 lat	0,1623	0,0472	12,28	<0,001	3,43	0,48–24,41
	10 lat	0,1623	0,0981	2,68	0,0017	1,65	0,23–11,75

Uzyskane wyniki wyraźnie wskazują na zwiększenie ryzyka kumulacyjnego występowania czerniaka skóry u biorców narządów litych objętych niniejszą analizą w okresie po przeszczepieniu, w porównaniu z ryzykiem kumulacyjnym w populacji ogólnej (ryc. 1).

Rycina 1. Częstość występowania czerniaka skóry u biorców przeszczepu wybranych narządów litych w Polce na podstawie danych Narodowego Funduszu Zdrowia za lata 2010–2022.



Trzeci artykuł cyklu również opiera się na danych pozyskanych z NFZ i KRN, tym razem jednak dotyczących ryzyka wystąpienia NMSC u biorców nerki, wątroby i serca w Polsce. Artykuł ten odpowiada trzeciemu ze wskazanych celów szczegółowych naszych badań. Dane obejmują 17 252 pacjentów po transplantacjach przeprowadzonych w latach 2010–2022. Przypadki NMSC w badanej grupie i populacji ogólnej zidentyfikowano na podstawie kodów ICD-10 (C44.0–C44.9).

W grupie biorców nerki, którą stanowiło 12 205 pacjentów, wykazano znaczne zwiększenie ryzyka rozwoju NMSC w porównaniu z ryzykiem w populacji ogólnej Polski. Roczna skumulowana zachorowalność na NMSC w grupie biorców nerki wynosiła 0,09%, natomiast w populacji ogólnej 0,04% ($p < 0,001$). W okresie 5-letnim od przeszczepienia tego narządu odnotowano ryzyko występowania NMSC na poziomie 0,83%, podczas gdy ryzyko populacyjne wynosiło w tym samym okresie 0,18% ($p < 0,001$). Z kolei 10-letnie ryzyko kumulacyjne zachorowania na NMSC po przeszczepieniu nerki wyniosło 4,18%, co również jest wynikiem znamiennie wyższym ($p < 0,001$) w porównaniu z ryzykiem populacyjnym, które w tym czasie wyniosło 0,36% (tab. 4).

Tabela 4. Wyniki testu Z i RR dla skumulowanej zapadalności na NMSC (C44) u biorców nerki w porównaniu z zapadalnością w populacji ogólnej.

	Okres obserwacji	Ryzyko kumulacyjne (%)		z	wartość p	RR	95% CI
		biorcy	populacja				
NMSC (C44)	1 rok	0,0857	0,0355	29,30	<0,001	2,41	1,29–4,48
	5 lat	1,2145	0,1774	240,71	<0,001	6,84	5,69–8,24
	10 lat	4,1835	0,3597	436,16	<0,001	11,63	10,27–13,17

W grupie pacjentów po przeszczepieniu wątroby, która liczyła 3584 pacjentów, także wykazano istotny statystycznie ($p < 0,001$) wzrost kumulacyjnego ryzyka zachorowania na NMSC w grupie biorców w porównaniu z ryzykiem populacyjnym w każdym z okresów obserwacji. Po roku wśród biorców odnotowano ryzyko wynoszące 0,09%, natomiast ryzyko populacyjne osiągnęło 0,04%. Po 5 latach obserwacji rozwój nowotworu odnotowano u 0,83% pacjentów, co było wartością również znamiennie wyższą od zachorowalności w populacji ogólnej, która w tym okresie wyniosła 0,18%. Po 10 latach obserwacji ryzyko kumulacyjne w grupie biorców wątroby wyniosło 2,65% *vs* 0,36% w populacji ogólnej (tab. 5).

Tabela 5. Wyniki testu Z i RR dla skumulowanej zapadalności na NMSC (C44) u biorców wątroby w porównaniu z zapadalnością w populacji ogólnej.

	Okres obserwacji	Ryzyko kumulacyjne (%)		z	wartość p	RR	95% CI
		biorcy	populacja				
NMSC (C44)	1 rok	0,0931	0,0355	17,67	<0,001	2,61	0,84–8,21
	5 lat	0,8311	0,1774	74,15	<0,001	4,68	2,99–7,35
	10 lat	2,6462	0,3597	112,44	<0,001	7,35	6,77–7,99

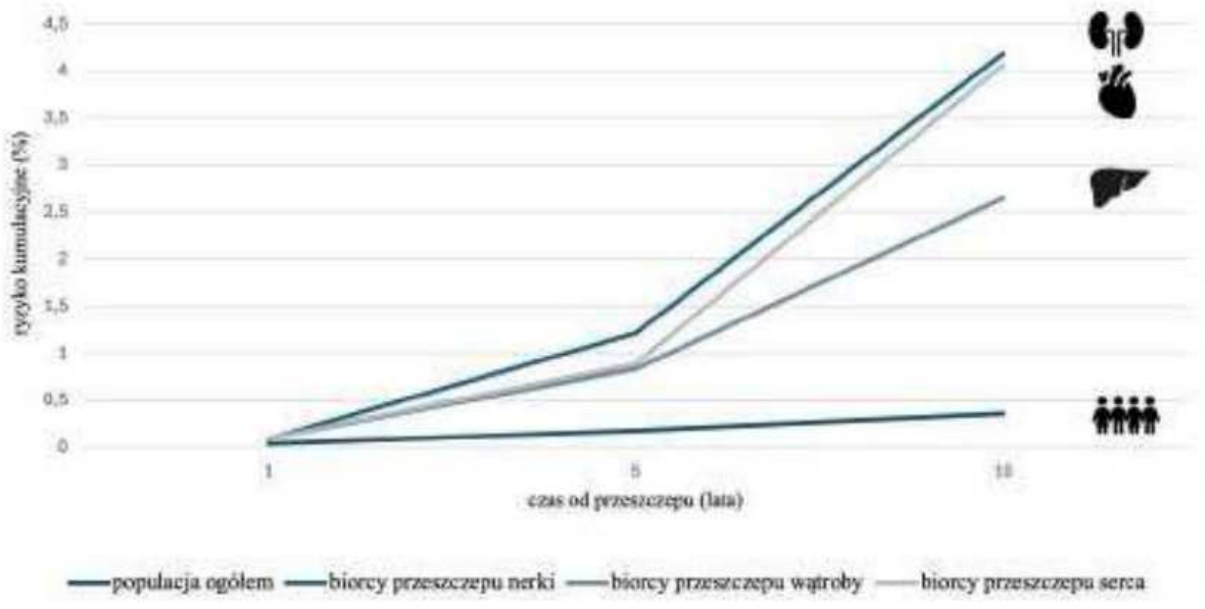
U 1418 biorców serca, których dane uwzględniono w analizie, również stwierdzono wyższą skumulowaną zachorowalność na NMSC w każdym z okresów obserwacji. Po roku ryzyko kumulacyjne w grupie biorców tego narządu wyniosło 0,09% *vs* 0,04% dla populacji ogólnej ($p < 0,001$). Po 5 latach zapadalność na NMSC w tej grupie pacjentów wyniosła 0,89%, natomiast w populacji ogólnej 0,18% ($p < 0,001$). Po 10-latach odnotowano NMSC u 4,06% pacjentów po przeszczepieniu serca, natomiast ryzyko populacyjne wyniosło 0,36% ($p < 0,00$) (tab. 6).

Tabela 6. Wyniki testu Z i RR dla skumulowanej zapadalności na NMSC (C44) u biorców serca w porównaniu z zapadalnością w populacji ogólnej.

	Okres obserwacji	Ryzyko kumulacyjne (%)		z	wartość p	RR	95% CI
		biorcy	populacja				
NMSC (C44)	1 rok	0,0909	0,0355	9,92	<0,001	2,56	0,37–18,18
	5 lat	0,8871	0,1774	42,08	<0,001	5,00	2,2
	10 lat	4,0609	0,3597	95,71	<0,001	11,29	9,64–13,22

Zwiększenie ryzyka wystąpienia NMSC było istotne statystycznie w każdej z grup, co jest zgodne z danymi światowymi i potwierdza konieczność monitorowania pacjentów po przeszczepieniu narządów (ryc. 2).

Rycina 2. Częstość występowania NMSC u biorców przeszczepu wybranych narządów litych w Polce na podstawie danych Narodowego Funduszu Zdrowia za lata 2010–2022.



Czwarta praca uwzględniona w niniejszej rozprawie doktorskiej to opis przypadku. Dotyczy on pacjenta, który od kilkudziesięciu lat stosuje leki immunosupresyjne w celu zapobiegania odrzuceniu przeszczepionej nerki. W toku obserwacji wielokrotnie rozpoznawano u niego niemelanocytarne nowotwory skóry SCC i BCC. Opis ten stanowi konkretną, indywidualną ilustrację problematyki będącej przedmiotem rozprawy doktorskiej, chociaż oczywiście jego wartość dowodowa jest marginalna. Jednakże artykuł podkreśla moje praktyczne, a nie tylko teoretyczne, zainteresowanie opisywanym zagadnieniem oraz obrazuje wagę zaleceń dla grupy pacjentów po przeszczepieniu narządu litego, które można sformułować na podstawie prezentowanych powyżej analiz. Z tych dwóch powodów, z pełną świadomością niskiej wartości dowodowej opisu pojedynczego przypadku, zdecydowałam się na dołączenie tego artykułu do cyklu prac wchodzących w skład rozprawy doktorskiej. Sądzę, że pozwala to spojrzeć na omawiany problem nie tylko w oparciu o wielkoskalowe badania na grupie >17 000 chorych, ale również poprzez pryzmat losów konkretnego chorego.

6. Wnioski z cyklu prac

Cykl publikacji wchodzących w skład niniejszej rozprawy doktorskiej opisuje zwiększenie ryzyka występowania nowotworów skóry u pacjentów po przeszczepieniu nerki, wątroby lub serca wraz z upływem czasu od transplantacji. Jest to pierwsza tego typu analiza epidemiologiczna uwzględniająca dane dla całej populacji Polski. Pozwoliła ona określić rzeczywiste ryzyko nowotworzenia w obrębie skóry w tej – stale rosnącej – grupie pacjentów w Polsce.

W dokonanym przeglądzie systematycznym piśmiennictwa i metaanalizie poddano szczegółowej ocenie wpływ stosowania CNI przez biorców przeszczepu nerki w kontekście ryzyka występowania CM i NMSC. Wyniki wskazują, że stosowanie CNI wiąże się jednoznacznie z większym ryzykiem wystąpienia CM oraz NMSC w porównaniu z alternatywnymi terapiami immunosupresyjnymi, które zawierają wyłącznie leki immunosupresyjne należące do innych grup. Wskazuje to na konieczność starannego doboru schematów immunosupresji, z uwzględnieniem tego ryzyka, a także na potrzebę systematycznej kontroli dermatologicznej pacjentów poddanych takiemu leczeniu.

Pozyskanie danych z NFZ i KRN pozwoliło na przeprowadzenie analizy epidemiologicznej dotyczącej ryzyka występowania CM u biorców nerki, wątroby lub serca w Polsce. W badaniu obejmującym ponad 17 000 pacjentów po przeszczepieniu wykonanym na przestrzeni lat 2010–2022 wykazano istotnie zwiększone ryzyko kumulacyjne wystąpienia CM w grupie biorców w porównaniu z ryzykiem populacyjnym. Dane wskazują, że w przypadku biorców nerki, wątroby i serca ryzyko wystąpienia CM jest łącznie dwukrotnie większe po roku, 4 razy większe po pięciu latach i prawie 9 razy większe po dziesięciu latach od przeszczepienia narządu w porównaniu z populacją ogólną Polski w tym samym czasie.

Pozyskana w ramach pracy doktorskiej obszerna baza danych pozwoliła również na wykonanie analizy epidemiologicznej, określającej skalę ryzyka występowania NMSC u biorców nerki, wątroby i serca. Uzyskane wyniki zestawiono z ryzykiem populacyjnym wystąpienia NMSC w Polsce w tym samym okresie, uzyskując rzeczywiste wielkoskalowe dane dla naszego kraju. Wyniki analizy wskazują, że w przypadku biorców nerki, wątroby lub serca łącznie ryzyko wystąpienia NMSC jest dwukrotnie większe po roku, 4,5 razy większe po pięciu latach i aż 9 razy większe po dziesięciu latach w porównaniu z populacją ogólną Polski w tym samym okresie.

Dane prezentowane w ramach niniejszego cyklu, mają istotne znaczenie dla transplantologii, dermatologii, onkologii i zdrowia publicznego w Polsce. Stanowią pierwsze krajowe opracowanie tej tematyki na tę skalę. Uzyskane informacje mogą stanowić podstawę do stworzenia wytycznych w zakresie monitorowania pacjentów po przeszczepieniu narządu litego pod kątem rozwoju nowotworów skóry. Regularne badania dermatologiczne oraz edukacja pacjentów w zakresie ochrony przeciwsłonecznej i samodzielnego badania skóry mogą się znacząco przyczynić do zmniejszenia częstości i opóźnienia występowania nowotworów skóry u biorców tych narządów. Wcześnie wykryte nowotwory skóry cechują się lepszym rokowaniem, a tym samym większą szansą na całkowite wyleczenie. Na podstawie powyższych artykułów opracowano publikację zbiorczą podsumowującą cykl badań stanowiących rozprawę doktorską [23], która może stanowić punkt wyjścia do opracowania wytycznych dla pacjentów po przeszczepieniu nerki, wątroby lub serca w zakresie kontroli dermatologicznej. Wzmożony nadzór onkologiczny w zakresie nowotworów skóry w tej grupie pacjentów pozwoli na wczesne wykrywanie oraz szybkie wdrożenie odpowiedniego leczenia tych zmian, co umożliwi wydłużenie życia i poprawę jego jakości w okresie po transplantacji.

7. Piśmiennictwo

Poniższe przypisy odnoszą się wyłącznie do pozycji bezpośrednio cytowanych w niniejszej rozprawie doktorskiej. Pozostałe źródła, stanowiące podstawę merytoryczną dyskusji w poszczególnych artykułach, znajdują się w bibliografiach publikacji wchodzących w skład rozprawy, które załączono powyżej.

1. Poltransplant. Pobieranie i przeszczepianie narządów w Polsce 2024 r. Available from: https://files.poltransplant.org.pl/Pobieranie_i_przeszczepianie_2024.pdf. Accessed April 9, 2025.
2. Global Observatory on Donation and Transplantation. International Report on Organ Donation and Transplantation Activities 2023. Available from: https://www.transplant-observatory.org/wp-content/uploads/2024/12/2023-data-global-report-17122024.pdf. Accessed April 9, 2025.
3. Lizakowski S., Rutkowski P.: Nowotwory u chorych o przeszczepieniu nerki. In: Rutkowski P, editor. Leczenie nerkozastępcze. Lublin: Czelej; 2007. p. 409–418.
4. Birkeland S.A., Storm H.H., Lamm L.U., 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. PMID: 7829213.
5. Collett D., Mumford L., Banner N.R., Neuberger J., Watson C.: Comparison of the incidence of malignancy in recipients of different types of organ: a UK Registry audit. *Am. J. Transplant*., 2010; 10 (8): 1889–1896.
6. Engels E.A., Pfeiffer R.M., Fraumeni J.F. Jr, et al.: Spectrum of cancer risk among US solid organ transplant recipients. JAMA, 2011; 306 (17): 1891–1901.

7. Bouwes Bavinck J.N., Hardie D.R., Green A., et al.: The risk of skin cancer in renal transplant recipients in Queensland, Australia: A follow-up study. *Transplantation*, 1996; 61 (5): 715–721. doi:10.1097/00007890- 199603150-00008.
8. Birkeland S.A., Storm H.H., Lamm L.U., et al.: Cancer risk after renal trans- plantation in the Nordic countries, 1964–1986. *Int. J. Cancer*, 1995; 60 (2): 183–189. doi:10.1002/ijc.2910600209.
9. Naldi L., Fortina A.B., Lovati S., et al.: Risk of nonmelanoma skin cancer in Italian organ transplant recipients: A registry- based study. *Transplantation*, 2000; 70 (10): 1479–1484. doi:10.1097/00007890-200011270-00015.
10. Acuna S.A.: 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. PMID: 30017342.
11. Que S.K.T., Zwald F.O., Schmults C.D.: Cutaneous squamous cell carcinoma: Incidence, risk factors, diagnosis, and staging. *J. Am. Acad. Dermatol*., 2018; 78 (2): 237–247.
12. 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. PMID: 10025742.
13. Granata S., Tessari G., Stallone G., Zaza G.: Skin cancer in solid organ transplant recipients: still an open problem. *Front. Med*., 2023; 10: 1189680. doi:10.3389/fmed.2023.1189680.

14. American Cancer Society. Basal and squamous cell skin cancer risk factors. 2009. Available from: https://www.cancer.org/cancer/types/basal-and-squamous-cell-skin-cancer/causes-risks-prevention/risk-factors.html. Accessed: August 15, 2024.

15. Yarosh D.B., Pena A.V., Nay S.L., Canning M.T., Brown D.A.: Calcineurin inhibitors decrease DNA repair and apoptosis in human keratinocytes following ultraviolet B irradiation. *J. Invest. Dermatol*., 2005; 125: 1020–1025. doi: 10.1111/j.0022-202X.2005.23858.x.

16. Kuschal C., Thoms K.M., Schubert S., Schäfer A., Boeckmann L., Schön M.P., et al.: Skin cancer in organ transplant recipients: effects of immunosuppressive medications on DNA repair. *Exp. Dermatol*., 2012; 21: 2–6. doi: 10.1111/j.1600-0625.2011.01413.x.

17. Syed-Ahmed M., Narayanan M.: Immune dysfunction and risk of infection in chronic kidney disease. *Adv. Chronic Kidney Dis.,* 2019; 26 (1): 8–15. doi:10.1053/j.ackd.2019.01.004.

18. Adamopoulos S., et al.: Immunity, inflammation and heart failure: their role on cardiac function. *Front Immunol.,* 2019; 10: 2315. doi:10.3389/fimmu.2019.02315.

19. Harwood C.A., Proby C.M.: Management of skin cancer in organ transplant recipients: a review. *Br. J. Dermatol.,* 2010; 162 (6): 1205–1210. Atypical, often aggressive nature of post-transplant skin cancers noted.

20. Baker R.J., Mark P.B., Patel R.K., et al.: Renal association clinical practice guideline in post-operative care in the kidney transplant recipient. *BMC Nephrol*., 2017; 18 (1): 174. doi:10.1186/s12882-017-0553-2. PMID: 28571571.

21. Polskie Towarzystwo Transplantacyjne. Zalecenia dotyczące leczenia immunosupresyjnego po przeszczepieniu narządów unaczynionych. Warszawa: Polskie

Towarzystwo Transplantacyjne; 2024. Dostępne online na: https://p-t-t.org/sites/scm/files/2025-01/Zalecenia_Immunosupresja_2024_%C5%9Brodek.pdfp-t-t.org+1p-t-t.org+1

22. Imko-Walczuk B., Ankudowicz A., Jaśkiewicz J., Lizakowski S., Dębska-Ślizień A., Rutkowski B.: Skin cancer in organ transplant recipients. *Dermatology Review/Przegląd Dermatologiczny*, 2011; 98 (2): 91–103.
23. Wysocki W.M., Kulbat A.: Where there's smoke, there's fire – a brief report on skin malignancy incidence in renal, heart, and liver transplant recipients in Poland. *Oncol Clin. Pract.,* 2024. doi:10.5603/ocp.103839.

8. Streszczenie w języku polskim

Wstęp i cel: Zwiększająca się liczba przeszczepień narządów litych prowadzi do wzrostu liczby pacjentów, którzy w okresie po przeszczepieniu są poddani dożywotniej terapii immunosupresyjnej. Stosowanie leków immunosupresyjnych, jak inhibitory kalcyneuryny, wiąże się z większym ryzykiem rozwoju nowotworów skóry, w tym czerniaka i niemelanocytarnych nowotworów skóry. Do tej pory nie przeprowadzono jednak badań z udziałem dużej liczby chorych dotyczących częstości występowania tych nowotworów u biorców narządów w Polsce. Głównym celem badania była analiza częstości występowania CM i NMSC u pacjentów po przeszczepieniu nerki, wątroby lub serca w Polsce oraz ocena wpływu immunosupresji na rozwój tych nowotworów.

Materiał i metody: Badanie łączy wyniki przeglądu systematycznego piśmiennictwa międzynarodowego oraz metaanalizy (obejmujących łącznie dane 309 551 pacjentów), dotyczących ryzyka rozwoju NMSC i MSC u osób po przeszczepieniu nerki leczonych CNI. Analizy dotyczące populacji polskiej bazowały na danych pozyskanych z NFZ oraz KRN na temat częstości występowania nowotworów skóry u biorców przeszczepów nerek, wątroby i serca, wykonanych w latach 2010–2022. Łącznie do analiz włączono dane dotyczące częstości występowania CM i NMSC u ponad 17 000 pacjentów po przeszczepieniach tych narządów i porównano z danymi dotyczącymi ogólnej populacji Polski.

Wyniki: Wyniki przeglądu systematycznego piśmiennictwa wykazały korelację między stosowaniem CNI u pacjentów po przeszczepieniu nerki a zwiększonym całkowitym ryzykiem nowotworów skóry (OR 1,28; 95% CI: 0,10–16,28; $p < 0,01$), ryzykiem MSC (OR 1,09; 95% CI: 0,25–4,74; $p < 0,01$) oraz ryzykiem NMSC (OR 1,16; 95% CI: 0,41–3,26; $p < 0,01$). Dane dotyczące populacji polskiej pochodziły z badań obejmujących ponad 17 000 pacjentów

po przeszczepieniu nerki, wątroby lub serca. W porównaniu z ogólną populacją, pacjentów po przeszczepieniu nerki charakteryzowało większe ryzyko CM po 1 roku (0,02% *vs* 0,01%, $p < 0,001$), po 5 latach (0,17% *vs* 0,05%, $p < 0,001$) oraz po 10 latach (0,36% *vs* 0,1%, $p < 0,001$). U chorych po transplantacji wątroby ryzyko wystąpienia CM wynosiło po 1 roku 0,03% *vs* 0,01% dla populacji Polski ($p < 0,001$), zaś po 5 latach i 10 latach odpowiednio: 0,20% *vs* 0,05% ($p < 0,001$) i 0,20% *vs* 0,1%, ($p < 0,001$). Również ryzyko wystąpienia CM u pacjentów po przeszczepieniu serca było wyższe, zarówno po 1 roku (0,02% *vs* 0,01%, $p < 0,001$), jak i po 5 (0,16% *vs* 0,05%, $p < 0,001$) oraz po 10 latach (0,16% *vs* 0,1%, $p < 0,001$). Ponadto, w populacji biorców nerki ryzyko wystąpienia NMSC wynosiło po 1 roku 0,09% *vs* 0,04% dla populacji ogólnej ($p < 0,001$) i odpowiednio 1,21% *vs* 0,18% ($p < 0,001$) oraz 4,18% *vs* 0,36% ($p < 0,001$) po 5 latach i 10 latach. Także u biorców wątroby ryzyko NMSC było większe w porównaniu z populacją ogólną: po 1 roku (0,09% *vs* 0,04%, $p < 0,001$), po 5 latach (0,83% *vs* 0,18%, $p < 0,001$) i po 10 latach (2,65% *vs* 0,36%, $p < 0,001$). W grupie pacjentów po przeszczepieniu serca ryzyko NMSC było wyższe w porównaniu do ryzyka populacyjnego po 5 latach (0,89% *vs* 0,18%, $p < 0,001$) oraz po 10 latach (4,06% *vs* 0,36%, $p < 0,001$).

Wniosek główny:

W Polsce pacjenci po przeszczepieniu narządów litych (nerki, wątroby, serca), poddawani przewlekłej immunosupresji, wykazują zwiększoną częstość występowania CM oraz NMSC w porównaniu z populacją ogólną. Wyniki te potwierdzają zasadność wdrażania ukierunkowanych działań profilaktycznych i monitorujących powstawanie nowotworów skóry w tej grupie pacjentów.

Wnioski szczegółowe:

1. Metaanaliza światowego piśmiennictwa medycznego wykazała, że inhibitory kalcyneuryny (cyklosporyna A, takrolimus) istotnie zwiększają ryzyko wystąpienia MSC i NMSC u biorców przeszczepów w porównaniu z chorymi poddawanym terapii innymi lekami immunosupresyjnymi, co podkreśla konieczność uwzględniania ryzyka onkologicznego przy doborze terapii immunosupresyjnej.
2. Analiza danych pozyskanych z NFZ i KRN umożliwiła po raz pierwszy wielkoskalową ocenę rzeczywistej zachorowalności na MSC w grupie chorych poddanych przeszczepieniu narządów litych w Polsce, potwierdzając wyraźnie zwiększone ryzyko nowotworzenia wśród biorców. Dane wskazują, że u biorców nerki, wątroby i serca ryzyko wystąpienia MSC jest łącznie dwukrotnie większe po roku, 4 razy większe po pięciu latach i prawie 9 razy większe po dziesięciu latach od wykonania przeszczepienia – w porównaniu z populacją ogólną Polski w tym samym okresie.
3. Analiza danych pozyskanych z NFZ i KRN wykazała, że u biorców nerki, wątroby lub serca mają ryzyko wystąpienia NMSC jest łącznie dwukrotnie większe po roku, 4,5 razy większe po pięciu latach i aż 9 razy większe po dziesięciu latach od przeszczepienia narządu –

   w porównaniu z populacją ogólną Polski w tym samym okresie.
4. Rekomenduje się stworzenie zintegrowanych programów profilaktycznych, obejmujących systematyczne kontrole dermatologiczne w grupie pacjentów po przeszczepieniu nerki, wątroby lub serca oraz działania edukacyjne skierowane do pacjentów i personelu medycznego w zakresie ochrony przeciwsłonecznej i samodzielnego badania skóry.

9. Streszczenie w języku angielskim

Introduction and Aim: The increasing number of solid organ transplants has led to a growing population of patients who, in the post-transplant period, are subjected to lifelong immunosuppressive therapy. The use of immunosuppressive drugs, such as calcineurin inhibitors (CNI), is associated with a higher risk of developing skin cancers, including melanoma and non-melanoma skin cancers (NMSC). However, no large-scale studies have yet been conducted on the incidence of these cancers among organ recipients in Poland. The main aim of this study was to analyze the incidence of melanoma (CM) and NMSC in patients after kidney, liver, or heart transplantation in Poland and to assess the impact of immunosuppression on the development of these cancers.

Material and Methods: The study combined the results of a systematic review of international literature and a meta-analysis (including data on a total of 309,551 patients), concerning the risk of NMSC and melanoma in kidney transplant recipients treated with CNI. Analyses for the Polish population were based on data obtained from the National Health Fund (NFZ) and the National Cancer Registry (KRN) on the incidence of skin cancers in kidney, liver, and heart transplant recipients between 2010 and 2022. In total, data on more than 17,000 patients were included in the analyses and compared with data from the general Polish population.

Results: The systematic review demonstrated a correlation between CNI use in kidney transplant patients and an increased overall risk of skin cancers (OR 1.28; 95% CI: 0.10–16.28; $p < 0.01$), risk of melanoma (OR 1.09; 95% CI: 0.25–4.74; $p < 0.01$), and risk of NMSC (OR 1.16; 95% CI: 0.41–3.26; $p < 0.01$). Data on the Polish population came from studies involving more than 17,000 kidney, liver, and heart transplant recipients. Compared with the general population, kidney recipients had a higher risk of melanoma after 1 year (0.02% vs 0.01%, $p < 0.001$), after 5 years (0.17% vs 0.05%, $p < 0.001$), and after 10 years (0.36% vs 0.1%, $p <$

0.001). In liver transplant recipients, the risk of melanoma was 0.03% vs 0.01% after 1 year ($p < 0.001$), 0.20% vs 0.05% after 5 years ($p < 0.001$), and 0.20% vs 0.1% after 10 years ($p < 0.001$). Similarly, in heart transplant recipients, the risk of melanoma was higher both after 1 year (0.02% vs 0.01%, $p < 0.001$), after 5 years (0.16% vs 0.05%, $p < 0.001$), and after 10 years (0.16% vs 0.1%, $p < 0.001$). In kidney recipients, the risk of NMSC was 0.09% vs 0.04% after 1 year ($p < 0.001$), 1.21% vs 0.18% after 5 years ($p < 0.001$), and 4.18% vs 0.36% after 10 years ($p < 0.001$). In liver recipients, the risk was 0.09% vs 0.04% after 1 year ($p < 0.001$), 0.83% vs 0.18% after 5 years ($p < 0.001$), and 2.65% vs 0.36% after 10 years ($p < 0.001$). In heart recipients, the risk of NMSC was also higher compared with the general population: after 5 years (0.89% vs 0.18%, $p < 0.001$) and after 10 years (4.06% vs 0.36%, $p < 0.001$).

Main Conclusion:

In Poland, patients after solid organ transplantation (kidney, liver, heart) undergoing chronic immunosuppression show an increased incidence of melanoma and NMSC compared with the general population. These results confirm the need for targeted preventive and monitoring measures for skin cancers in this patient group.

Detailed Conclusions:

1. The meta-analysis of global medical literature showed that calcineurin inhibitors (cyclosporine A, tacrolimus) significantly increase the risk of melanoma and NMSC in transplant recipients compared with patients treated with other immunosuppressive agents, highlighting the need to consider oncological risk when selecting immunosuppressive therapy.
2. Analysis of NFZ and KRN data enabled, for the first time, a large-scale assessment of the actual incidence of melanoma in Polish solid organ transplant recipients, confirming a clearly increased cancer risk in this group. The data indicate that in kidney, liver, and heart recipients, the risk of melanoma is twice as high after 1 year, 4 times higher after 5 years, and nearly 9 times higher after 10 years compared with the general Polish population in the same periods.
3. Analysis of NFZ and KRN data also showed that kidney, liver, and heart recipients face a risk of NMSC that is twice as high after 1 year, 4.5 times higher after 5 years, and up to 9 times higher after 10 years compared with the general Polish population in the same periods.
4. It is recommended to establish integrated preventive programs, including systematic dermatological examination for kidney, liver, and heart transplant recipients, as well as educational initiatives aimed at patients and medical staff on sun protection and self-examination of the skin.

10. Zestawienie skrótów i skrótowców stosowanych w pracy

Skrót/Skrótowiec	Objaśnienie
BCC	*basal cell carcinoma* – rak podstawnokomórkowy skóry
CI	*confidence interval* – przedział ufności
CNI	*calcineurin inhibitor* – inhibitor kalcyneuryny
CM	*cutaneous melanoma* – czerniak skóry
HPV	*human papillomavirus* – wirus brodawczaka ludzkiego
KRN	Krajowy Rejestr Nowotworów
MNiSW	Ministerstwo Nauki i Szkolnictwa Wyższego
MSC	*melanoma skin cancer* – melanocytarne nowotwory skóry
NFZ	Narodowy Fundusz Zdrowia
NMSC	*non-melanoma skin cancer* – niemelanocytarny rak skóry
NNH	*number needed to harm* – liczba pacjentów, których poddanie danej interwencji (np. leczeniu) przez określony czas, wiąże się z wystąpieniem jednego dodatkowego niekorzystnego punktu końcowego
OR	*odds ratio* – iloraz szans
P	*p-value* – wartość statystyczna określająca istotność testu
RR	*relative risk* – ryzyko względne
SCC	*squamous cell carcinoma* – rak płaskonabłonkowy skóry
UAFM	Uniwersytet Andrzeja Frycza Modrzewskiego
USA	*United States of America* – Stany Zjednoczone Ameryki
UV	*ultraviolet radiation* – promieniowanie ultrafioletowe
vs	*versus* – przeciw, w porównaniu do (łac., powszechnie używane w analizach statystycznych i medycznych)
WHO	*World Health Organization* – Światowa Organizacja Zdrowia