Is there an association between long-term immunosuppressive therapy and skin cancer risk in kidney transplant recipients? A Systematic Review of the literature

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Abstract

Background: Kidney transplant recipients require long-term immunosuppressive therapy, increasing susceptibility to secondary conditions. This systematic review explored the association between immunosuppression use and skin cancer risk in post kidney transplant patients.

Research Design: Systematic Review (SR) including Randomised Controlled Trials (RCT) and Cohort Studies. The databases (Medline, CINAHL, Embase) were searched and a total of 29 studies were included.

Results: Findings were presented using narrative synthesis. Evidence identified a significant association between long-term immunosuppression and increased skin cancer risk.

Conclusion: Alternative immunosuppressive strategies should be considered for those known to be higher risk. Individualised treatment and enhanced monitoring are recommended, with further research needed.

Introduction

Skin cancer is one of the most common cancers globally, with melanoma (MM) and non-melanoma skin cancer (NMSC) being the most prevalent. Kidney transplant recipients are at substantially higher risk due to the long-term immunosuppression use. Up to 45% develop skin cancer within 10 years, rising to 80% at 20 years post-transplant. Yet despite the known risks, screening and awareness remain inconsistent in clinical practice. This study investigates the link between different immunosuppressive therapies used in renal transplant patients and the skin cancer risks, to further inform clinical care.

Question: Using the PICO framework to guide formulating a question - ***Is there and an association between long-term immunosuppressive therapy and skin cancer risk in kidney transplant recipients?***

Aim: To explore the risks associated with long-term use of immunosuppression in kidney transplant patients.

The primary objectives were:

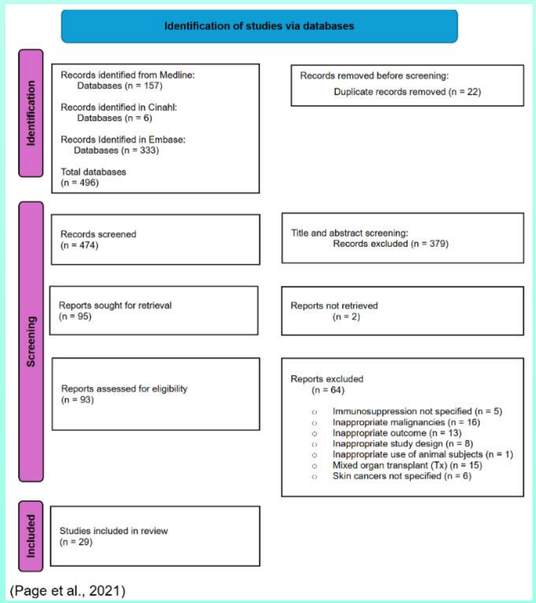
1. To evaluate associated studies investigating the use of immunosuppression in post-kidney transplant patients
2. To assess the quality of the studies used within this review, using the CASP tool (Critical Appraisal Skills Programme) for both RCTs and cohort studies
3. To evaluate the risk of bias of the chosen studies within this review, utilising ROB2 (Risk Of Bias Tool)
4. To examine the direct link between the use of immunosuppression and the risk of developing skin cancer
5. To examine existing literature and to determine the need for future research

Methodology

The search strategy was developed by revisiting the PICO framework.

PICOS	Inclusion criteria	Exclusion criteria
Population – 'Adults with a history of a kidney transplant'	. Adults only >18 years . Had a solid kidney organ transplant	. <18 years old . Any other solid organ transplant
Intervention – 'Long-term immunosuppression use'	. Immunosuppression therapy for solid kidney organ transplantation	. No immunotherapy use
Comparison – 'None'	Not applicable	Not applicable
Outcome – 'An increased risk of developing skin cancer '	. Melanomas . Non-melanoma skin cancer (NMSC), including basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) . Formal diagnosis of skin cancer . Merkel cell carcinoma	. T cell lymphoma of the skin . Sebaceous gland cancer . Bowen's disease . Kaposi's sarcoma . No diagnosis of skin cancer or skin lesion
Study design	. Randomised control trials . Quantitative research . Cohort studies	. Policies . Reviews . Case studies . Systematic reviews . Qualitative research . Conference Abstracts
Publication characteristics	. Published within the last 10 years . Peer reviewed . Published in English language only	. None peer reviewed . Published in other languages . Published before 2015 . Repetition

496 Initial studies were included for further screening. After screening a total of 29 studies were eligible to be included for review. Focus was on quantitative evidence, including Randomised Control Trials (RCTs) and cohort studies. The PRISMA framework (Figure 1) was used to illustrate the selection process. For quality appraisal, the CASP tool was used, incorporating a scoring system based on12 questions for cohort studies and 11 questions for RCTs. Application of the CASP appraisal tool enabled systematic organisation of the included studies according to methodological quality and risk of bias, thereby enhancing the accuracy and credibility of the review findings.



(Page et al., 2021)

Figure 1: PRISMA

Results

Included RCTS

Author and title of study	Background	Methodology	Participants	Results	Limitations
Ying et al. (2018) De novo or early conversion to everolimus and long-term cancer outcomes in kidney transplant recipients: A trial-based linkage study.	Focus on the incidence of NMSC in KTRs on different classes on immunosuppression therapy EVL immunosuppression compared to triple therapy of CNI, MPA and corticosteroids This study is a long term follow up of RCT participants	Trial based linage study – outcomes of participants were incorporated alongside a data registry (ANZDATA) Using RCTs and prospective studies Located in Australia and New Zealand	Total of 192 randomised to EVL (131 to a reduced dose and 61 to a withdrawal. 87 were randomised to either CSA or TAC and MPA	30 EVL patients developed NMSC (16 SCC, 14 BCC) VS control group 17 (8 SCC, 9 BCC) A reduced exposure to CNI-based triple therapy and those that were randomized to EVL, had a 56% reduction in NMSC post-transplant MPA was not associated with increased risks of NMSC Age was the greatest risk associated with the development of NMSC in patients on EVL	This study recognised that some data may have been missing due to unpublished data or small centre research not being captured – risk for publication bias Only first episodes on NMSC documented – potential for missing data that is crucial for the overall long-term risk

Included Cohort Studies

	Background	Methodology	Participants	Results	Limitations	CASP
Kaufmann et al. (2016) Epithelial Skin cancers after kidney transplantation: A retrospective single-centre study on 376 recipients	The occurrence of rates of NMSC in KTRs. The multiple factors associated are explored, including the immunosuppressive agents prescribed. These are examined to identify the increased risks in this patient group	Retrospective cohort Located in Switzerland Data collected over 39 years (1970-2009) From 2002 patients were examined for changes	376 KTRs: 233 males, 143 females from retrospective data	This study identified that the most frequently prescribed treatments were prednisolone (89.3%), CSA (81.9%), MMF (35.5% and AZA (32%) Total of 89 (23.67%) development NMSC CSA and TAC showed an association with NMSC – a x2.81 increase to risk 20 years post immunosuppression use, increased risk in males, rather than females (74% more likely) and was more associated with SCC (x3.3 increased risk)	Potential for the risk of recall bias and incomplete information. This is due to risks of patients not remembering past events during follow up examinations, for example premalignant lesions Extensive time for data collection. This could alter results, as over an extended period, there are changes occurring globally including global warming, changes in sun protection habits and more in depth patient education on the risks	14/14
Crespo et al. (2017) Effector Antitumor and Regulatory T Cell Responses Influence the Development of Nonmelanoma Skin Cancer in Kidney Transplant Patients	Immune cell responses to CNI and the contribution to SCC VS conversation to mTOR-i as potential protection	Cross-sectional observational study with prospective analysis Located in Barcelona, Spain	Total of 90 participants 59 KTRs cross sectional analysis with SCC on CNI 25 with SCC on mTOR-i 25 KTRs with SCC were on switched to EVL and reviewed after 1 year	CNI use showed impaired T cell response and predicted SCC Recovery of protective T cells when switched over the mTOR-i	Low number of patients assessed during switch of immunosuppression Absence of clinical follow up	7/14

Overall, there was strong evidence of a positive association between immunosuppression and skin cancer, with non-melanoma skin cancer (NMSC) being acknowledged as more common than melanoma, especially squamous cell carcinoma (SCC). The absolute risk for the development of NMSC increases by 27.9% from pre-kidney transplant to post-transplant. The risk has been identified as increasing with the duration of immunosuppression, the use of calcineurin inhibitors (CNI) and azathioprine. However, some evidence suggests that mammalian target of rapamycin (mTOR) inhibitors may reduce the overall risk. However, the immunosuppressed patient continues to show higher incidences and a greater severity and metastasis risk.

Conclusion

The findings of the studies included in the SR are consistent, indicating that long-term immunosuppressive therapy in kidney transplant patients is significantly associated with increased skin cancer risk. The overall risk is influenced by the type of medication and the duration of therapy. The findings highlight the need for improved monitoring and clinical awareness.

Limitations

This SR was conducted by an independent researcher, which is viewed as a limitation due to potential risks of subjective interpretation. It is recommended to involve dual researchers to execute the rigorous review process. Additionally, the included studies had various data collection methods, with some collecting data for over 20 years. While this offers substantial contextual information on the overall incidence of skin cancer, it is important to recognise that sun habits have changed over time. Overtime, alterations in the ozone layer, has led to increased UV exposure. Alongside this, shifts in medication use also have to be considered.

Recommendations

1. Implement routine skin cancer screening protocols
2. Increase staff education and awareness
3. Promote patient education on UV exposure and self-monitoring
4. Consider alternative immunosuppressive regimens (e.g., mTOR inhibitors)
5. Strengthen multidisciplinary collaboration (renal + dermatology)
6. Conduct further empirical research

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