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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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Declaration

I hereby declare that this thesis is my own work and effort and that it has not been submitted elsewhere for any award. Where other sources of information have been used, they have been acknowledged.

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Abstract

Introduction: Renal transplant patients are at an increased risk for other complex health conditions linked to long-term immunosuppression therapy. The occurrence of skin-related cancers is becoming more common within this patient group.

Aims: This systematic review aims to explore the relationship associated with the long-term use of immunosuppression in kidney transplant patients and the development of skin cancer among these patients.

Methods: This review searched the following databases: Medline, Cinahl, and Embase, to compile the most recent research on skin cancer risks in patients on long-term immunosuppression. The inclusion criteria included peer-reviewed studies with quantitative data, such as randomised controlled trials and cohort studies. A total of 29 studies were included.

Results: The results showed that there is substantial evidence supporting the association between the use of immunosuppression and the implications for overall skin cancer risk.

Conclusion: Long-term immunosuppression use after a kidney transplant is correlated with increased risks for skin cancer development. The selection of immunosuppressive treatment should be individualised, and alternative immunosuppressive strategies should be considered for patients who are known to be at higher risk for developing skin cancer. However, further prospective studies are needed to expand upon existing findings.

Chapter 1: Introduction & Background

This dissertation aims to explore the relationship associated with the long-term use of immunosuppression in kidney transplant patients and the development of skin cancer among these patients. This chapter aims to enhance understanding of kidney failure, the immunosuppressive therapy used after kidney transplantation, the prevention of kidney graft rejection, and the skin cancer risks associated with this patient population.

1.1 Introduction

The rates of skin cancer among the general public continue to be one of the most recognised forms of cancer, currently ranking 17th as the most common cancer worldwide (World Cancer Research Fund, 2024). The specific skin-related cancers often observed are malignant melanoma (MM) and non-melanoma skin cancers (NMSC), which include basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) (Kohnehshahri et al., 2023). It has been statistically shown that NMSC shows a higher rate of new cases than MM cases, yet MM continues to be on an upward trend, affecting all year ranges (Cancer Research UK, 2022; Cancer Research UK, 2023a). It is understood that the most common causes for these types of skin cancer include advanced ultraviolet (UV) exposure, geographical status, lifestyle, genetics, age and ethnicity. Furthermore, there is a common perception that the use of long-term immunosuppressive therapy has a crucial impact on a skin cancer diagnosis, leading to national guidance and recommendations being put into action to protect these patients (Cancer Research UK, 2023b; Kohnehshahri et al., 2023).

Worldwide, kidney failure patients who have undergone a solid organ transplant are susceptible to developing various pathological diseases and adverse side effects post-transplant due to the use of immunosuppressants (Hussain & Khan, 2022). Research has recognised the association between solid organ transplants and skin cancer as one of the most common, potentially exceeding the risk compared to the general public (Sułowicz et al., 2017). Statistics highlight the connection between the immunosuppressive medications used and skin cancer in solid organ transplants,

showing that up to 45% of patients will receive a formal diagnosis of skin cancer within 10 years of transplant, and up to 80% twenty years post-transplant (International Transplant Skin Cancer Collaborative, 2025a). The use of immunosuppressants in these solid organ transplant patients not only increases their risk of skin cancer but also dramatically reduces survival rates due to the high occurrence of metastasis (Kreher et al., 2023). This highlights the importance of awareness and close monitoring of these patients post-transplant to mitigate their risks. After a review of the literature, it was noticed that there was scarce research locally surrounding kidney-transplant patients. From personal experience, there appears to be inadequate surveillance strategies or a lack of staff training within the renal unit for recognising these skin conditions in patients after transplantation. This may be due to a lack of awareness about the links between skin cancers and immunosuppressant use. Other contributing factors, such as inadequate staff education for lesion assessment, prolonged referral waiting times, and the absence of a direct link between the local dermatology unit and the renal unit for monitoring purposes, may also contribute to the issue.

In research, as professionals, it is recognised that there is an ongoing necessity to integrate evidence-based practice. Continuous research generates new knowledge, enhancing professional judgment and overall improving patient outcomes (Chien, 2019). Healthcare professionals must strive to avoid malevolent practices while remaining mindful of how a lack of knowledge, awareness, and incorrect management strategies can impact patient care. Patients should have continual access to multidisciplinary team services that adopt a holistic approach to their long-term conditions. It is understood that solid organ transplant patients are at a significantly higher risk for other diseases due to the use of immunosuppressants, leading to additional complexities and a poorer quality of life (De Pasquale et al., 2014; McKeaveney et al., 2020). In addition to providing holistic care, patients should receive appropriate assessment, screening protocols, and the integration of relevant management tools. Although it has been recognised that insufficient screening protocols may be a leading factor in impairing patient outcomes (Cordaro et al., 2020), the focus should be on how, as professionals, we can understand and become more aware of the crucial issues. This mainly concerns certain medication use that can potentially cause patients to experience a range of negative outcomes.

Therefore, there is a need to understand the direct risks involved, which contribute to the importance of proper assessments, screening protocols, educational strategies, and monitoring guidelines becoming embedded into practice. This will enable healthcare professionals to follow a holistic care approach while reducing risks and improving patient safety.

This review will examine the current evidence supporting the use of long-term maintenance immunosuppressive therapy in post-kidney transplant patients and the incidence of skin cancer in these patients. This will simultaneously provide high-quality and up-to-date information to help healthcare providers make formal and effective choices within their clinical practice to support the ongoing care, assessment and management of these patients within clinical settings (Higgins et al., 2024).

1.2 Background

1.2.1 Kidney Failure

Kidney failure has been defined by the National Kidney Foundation (2023) as ‘End Stage Kidney Disease’ (ESKD) and having a reduced kidney function of around 85-90%. This leads to the individual having to have dialysis or kidney transplantation for survival, with a kidney transplant ideally being favoured as the chosen therapy for ESKD (Fallahzadeh et al., 2014; Szumilas et al., 2023). Kidney transplants were initially attempted decades ago in the early 1900s. The first ever successful kidney transplant was in 1954, lasting a successful 8 years without the use of immunosuppressive therapy (Waring Historical Library, n.d.). The outcome of this transplant continued to raise questions as to whether there was more scope for the prevention of graft rejection over a longer period, which led to the disclosure of the use of graft irradiation in 1958 (Barker & Markmann, 2013). There continued to be a considerable amount of effort made over the following years, with researchers at the time seeking a broader understanding of antibodies and immunology in allowing for kidney transplant survival (Tantisattamo et al., 2022). This led to the use of the first

immunosuppressive drug alongside a steroid treatment for preventing kidney organ transplant rejection from 1962 to 1963 (Tantisattamo et al., 2022; Waring Historical Library, n.d.). Modern-day medicine has significantly advanced since the first initial steps, with the use of local graft irradiation still considered a successful second-line treatment following the failed attempts of conventional anti-rejection treatment (Fallahzadeh et al., 2014).

The risk of kidney transplant rejection has been dramatically reduced due to the use of modern-day maintenance immunosuppressive treatments, which regulate immune response (Szumilas et al., 2023). However, that does not make the risk of transplant rejection impossible. Initially, the donated kidney is transplanted from donor to recipient and is matched through an extensive biological process and compatibility tests by determining blood and tissue types (National Kidney Registry, 2025). Transplantation falls into two categories: living donor and deceased donor. Risk factors for rejection are noted from pre-transplant surgery. Factors such as graft function of the deceased or living kidney and individual characteristics such as age, ethnicity, and lifestyle for both the donor and recipient become a risk (Oweira et al., 2022). While both donor types have the potential for risks post-transplant, Ma et al. (2014) report that deceased donor-specific transplants hold higher rates of issues associated with poor graft function. Additionally, there is an inflammatory process, which may lead to adverse effects such as the contribution to cancer (Ma et al., 2014). Although some factors may be unavoidable, the awareness of these potential limiting factors will influence how graft failure risks can ultimately be reduced. Additionally, other diseases that lead to poor outcomes for patients post-transplantation need to be accounted for.

The attempts made throughout the years for human kidney transplant have evolved from being ‘impossible’ to being made ‘possible’, with immunosuppressive therapy continuing to develop and being the gold standard regarding treatment (National Institute for Health and Care Excellence [NICE], 2017). This leads to kidney survival becoming well-tolerated and rejection becoming a reduced risk (NICE, 2017; Szumilas et al., 2023). Chronic rejection significantly impacts patients; therefore, patients must adhere to medication for long-term graft survival. It is understood that poor optimisation of post-transplant medication has adverse effects on the outcome

of the transplanted kidney. Poor medication optimisation can also be recognised for its contribution to drug-related toxicities and pathological disease manifestations (Cheung & Tang, 2022). Rejection continues to be the primary concern regarding the optimisation and patient compliance of post-transplant immunosuppressants (Cheung & Tang, 2022). However, challenges continue to arise concerning the long-term use of immunosuppressive medications and their correlation with cancers post-transplant (Massicotte-Azarniouch et al., 2024).

1.2.2 Immunosuppression

The immune system acts as a defence system for the body and ultimately protects the body against infections and foreign bodies, further preventing exposure to different illnesses (Yatim & Lakkis, 2015). The immune response is triggered by memory storage, causing the body to continue fighting diseases while mitigating the pathogens from being able to make a host in the body (Institute for Quality and Efficiency in Health Care, 2023). For patients who have undergone a kidney transplant, an immune response naturally occurs, leading to inflammation and the activation of various immune cells and antibodies. This ultimately acts as a protective measure against the ‘foreign body’, and as a result, the body rejects the kidney (Yatim & Lakkis, 2015). This immune response to transplantation is primarily known as the ‘alloimmune response’ (Naik & Shawar, 2023). It is in this situation, without the use of pharmaceutical assistance, that the body becomes inflamed, initiating an innate immune response to fight the infection. Based on this, a more advanced system known as the adaptive system seizes control, leading to the activation of the acute rejection stage of this ‘foreign body’ (Szumilas et al., 2023). This response can occur from minutes to years post-transplant (Szumilas et al., 2023), hence sufficient controls must be in place to prevent the rejection of the transplanted organ (Naik & Shawar, 2023). The use of immunosuppressants primarily reduces the severity of the immune response to allow the transplanted kidney to serve its purpose (Hussain & Khan, 2022).

Clinical practice guidelines recommend closely monitoring patients in a post-transplant clinic after surgery. Routine appointments are scheduled every 2 to 3

weeks for the first month post-transplant, followed by 1 to 2 times a month for the following 2 to 3 months (Baker et al., 2017). The monitoring of these patients gradually decreases depending on the individual and any complications that may arise. Despite this, regular monitoring continues every 3 to 6 months thereafter (Baker et al., 2017). Due to the local renal unit being on a small island, transplants usually occur overseas in the United Kingdom. Patients are monitored for 6 weeks before returning to the island for routine monitoring in the post-transplant clinic, which is run by the specialist nurse and consultant. In these clinics, patients' blood is monitored for overall kidney function and the therapeutic monitoring of the immunosuppressive therapy (Han & Lubetzky, 2023; Wadhawan & Gupta, 2023). These services are required to follow core standards and provide high-quality care to patients in a timely, efficient and patient-centred manner while adhering to the best guidance (Kidney Research UK, 2019). The appropriate service will have specialist nurses and consultants closely monitoring the patient's crucial markers. However, these services may be neglecting the overall holistic care of patients due to not having a full, comprehensive understanding of all of their physical, emotional, mental, and psychosocial needs (McKeaveney et al., 2020). In turn, this can lead to patients having distorted perceptions of reality, mismanaging their new lease on life, and developing inappropriate habits. This not only affects patients' graft function but also their overall quality of life, which in turn potentially leads to the manifestation of multiple diseases (De Pasquale et al., 2014). The renal services are in high demand; therefore, staff may ultimately only have the capacity to focus on the recommended standards for the ongoing care of transplant patients. Following a holistic assessment approach is important, but it may be challenging to implement. Whilst the physical monitoring of the immunosuppressant levels through peripheral blood tests and identifying any risks for rejection is essential during these clinics, an essential part of the monitoring process is potentially being overlooked. This alone may emphasise a significant issue for the ongoing level of care of patients. A study by McKeaveney et al. (2020) illustrates how the patient experience post-transplant reveals an 'unmet care need' within these services. This demonstrates the demand for a more holistic approach in these assessment clinics. Due to the risks associated with medication use post-transplant, multidisciplinary teamwork is essential, factoring in continual assessment and support for potential lifestyle changes. As a result, this

approach will lead to better outcomes for patients regarding their overall quality of life (Baker et al., 2017; De Pasquale et al., 2014; McKeaveney et al., 2020).

The immunosuppressive therapy prescribed following transplant surgery is intentionally used to preserve the transplanted kidney. This prevents rejection while the body's natural defences respond to this as a mechanism against rejection (National Kidney Foundation, 2024). It is recommended that the treatment options for patients post-kidney transplant be tailored and benchmarked for appropriate use. Additionally, patients should be monitored long-term for adequate medication dosage and to assess for any graft rejection (Baker et al., 2017; NICE, 2017; Szumilas et al., 2023). The immunosuppression considered for use after kidney transplant is categorised into three stages: (a) Induction therapy, used as an intermediate immunosuppressant at the time of transplantation; (b) Initial maintenance therapy, used immediately post-transplant for around 3 to 6 months; and (c) Long-term maintenance therapy, which is introduced over a longer period, however at a lower dose (NICE, 2017). This systematic review will only examine the long-term maintenance therapy medications used in kidney transplant patients. The numerous types of long-term immunosuppressants most commonly recognised for use in kidney transplant patients include: (a) calcineurin inhibitors (CNIs), cyclosporine and tacrolimus; (b) mammalian target of rapamycin inhibitors (mTOR-i), sirolimus and everolimus; (c) antiproliferatives, azathioprine and mycophenolate; (d) glucocorticosteroids; and (e) biologics (Szumilas et al., 2023). Locally, CNIs are the preferred therapy, with tacrolimus being the favoured option. Although CNI medication is well-supported for short-term use to enhance graft survival, the evidence suggests a presumed risk of toxicity and the potential for tumour growth with long-term use (Smith et al., 2017). Despite the commitment to reducing the patient’s risk of kidney rejection, these immunosuppressive regimens amplify other risks to patients and what they may ultimately be predisposed to (Pisano et al., 2024). There continues to be strong evidence regarding the increased risks, specifically for toxicity, vascular issues, adverse reactions, and the emergence of pathological conditions such as diabetes (Wiseman, 2016). While indeed these risks are valid, it continues to be well-supported that patients have a higher prevalence of skin cancers and an overall increased risk of mortality alongside immunosuppressant use (Kreher et al., 2023; Massicotte-Azarniouch et al., 2024; Rollan et al., 2022).

It has been observed that the immune system, particularly in older individuals, may have an exacerbated inflammatory response, contributing to their increased risk of such cancers (Ma et al., 2014). Current evidence has shown that the risks for any age group are substantial, which undermines the protective role of the immune system and consequently allows cancer-producing cells to proliferate (Kohnehshahri et al., 2023). Therefore, while the understanding of how immunosuppressant medication functions at a cellular level is complex, the overall goal is to inhibit this immune response (Hussain & Khan, 2022). The specific types of immunosuppressants used for long-term maintenance therapy differ in their cellular mechanisms. Some immunosuppressants are known to have a higher risk of unwanted outcomes and potentially irreversible effects, thus being disregarded as long-term treatments if close monitoring and dose titration are not implemented (Hussain & Khan, 2022; Meneghini et al., 2021). The research highlights notable findings regarding the selection of long-term immunosuppressants, which are associated with an increased risk of developing skin cancers. This is particularly with the use of CNI medications and the antiproliferative agent azathioprine (Cegielska et al., 2018; Rollan et al., 2022). This raises concerns about CNI being the first-line medication in many cases, especially as the preferred choice at a local level. A review of the literature demonstrates that switching to another immunosuppressant option may reduce the risks linked to the recurrence of skin cancers (Cegielska et al., 2018). While the evidence appears promising, it is crucial to continue reviewing and evaluating the choice of immunosuppressants and their direct relationship with skin cancer.

1.2.3 Skin cancer

The skin is the largest organ in the body, serving as a barrier against daily aggressors, potential toxins, and infections (Kohnehshahri et al., 2023; Roky et al., 2025). The general population face numerous challenges regarding skin health, from childhood through adulthood and into older age. Many skin conditions arise from contact with our external environment and physiological changes, including infections and inflammatory diseases. These can lead to adverse reactions over

time, such as organ dysfunction, mental health issues, an increased risk of various cancers, and premature death (Bolognia et al., 2016). These skin conditions continue to significantly burden society and negatively impact patients' quality of life as well as their mental and physical health (Seth et al., 2017). Yet, skin cancer alone continues to be particularly prevalent globally (Roky et al., 2025). This situation highlights the importance of both staff and patient education about the detrimental factors influencing the diagnosis of such diseases. There is a need for greater emphasis on how research plays a crucial role in understanding these factors and providing guidelines for effective management (Hay et al., 2015; Seth et al., 2017).

A local Channel Island public health report isolated both MM and NMSCs within the higher bracket for diagnosis and mortality compared to that in the United Kingdom (Government of Jersey, 2024a). The report highlights how the geographical factor is considerably considered, possibly due to the stronger UV radiation. Global statistics from the International Agency for Research on Cancer (2024a) observed MM skin cancers in the general population to rank 17th in incidence and 22nd in mortality, while NMSCs rank 5th in incidence and 22nd in mortality (International Agency for Research on Cancer, 2024b). The International Agency for Research on Cancer (2025) estimates that by 2025, the incidence of NMSC will rise by 5.3%, and overall mortality will increase by 5.8%, while MM is projected to grow by 4.3% in incidence and 4.7% in mortality. Despite other major factors, immunosuppression is still reported to have a '3.6 fold' higher rate of skin cancer development, specifically with MM (Wunderlich et al., 2024). It is important to consider that Merkel cell carcinoma (MCC), another form of skin cancer, has been linked to immunosuppression usage with generally poorer outcomes (Ma & Brewer, 2014). It has been indicated that MCC has an overall 45% mortality rate and exceeds the incidence of MM. However, while MCC has been considered as an aggressive form of cancer, it has also been classified as a rarer variant of skin cancer compared to MM (Ma & Brewer, 2014; Roky et al. 2025). Rollan et al. (2022) reported in their research the severity of skin cancers whilst using immunosuppression. Findings indicated distinct numbers for the total registry of skin cancer-derived malignancies; 60.2% cutaneous squamous cell carcinoma (cSCC), 34% basal cell carcinoma (BCC), 4.95% MM and 0.75% Kaposi's Sarcoma (KS) (Rollan et al., 2022). While KS is important to consider due to the increased risk to the immunocompromised patient, this review will omit this from the

inclusion criteria. This is due to it being directly linked to endothelial cells, which line blood vessels and lymph nodes and not the skin cells directly (Cancer Research UK, n.d; Roky et al., 2025).

Feedback from the local report identified how the interpretation of these types of cancers will help to formally address strategies that can be implemented to help reduce the rates and minimise risks associated (Government of Jersey, 2024b). Nevertheless, it remains difficult when trying to determine the accurate cause of these skin cancers in immunosuppressed individuals due to poor patient engagement, staff and patient awareness, education and individual compliance during pre and post-screening (Cordaro et al., 2020). As a result, this may lead to the disregard of other potential factors that may have been precursors to any lesions or skin abnormalities observed post-transplantation. Therefore, it must be acknowledged that it is not the sole responsibility of the clinician, as in turn, patients must be held accountable if they do not follow clinical advice. For example, their awareness of extensive UV exposure within their particular patient demographic.

1.2.4 The immunocompromised patient and skin cancer

Many factors contribute to the risks faced by patients. The increased incidence of skin cancer in individuals undergoing the use of long-term immunosuppressive therapy continues to be consistently reinforced (Rollan et al., 2022). Whilst there is ongoing awareness that the protective ability of the immune system is weakened through immunosuppressive medication (Kohnehshahri et al., 2023). Several primary drivers contribute to the increased risk of skin cancers in immunocompromised patients, and some of these factors need to be considered during patient screening and monitoring. It has been observed that patients may be at a higher risk of skin cancers before kidney transplantation. Massicotte-Azarniouch et al. (2024) recognised that ESKD is an attributable factor in the development of cancer. Nonetheless, significant factors widely acknowledged to contribute to the heightened risks of skin cancer include prolonged exposure to UV radiation, genetic predisposition, ethnicity, education and screening protocols (Massicotte-Azarniouch et al., 2024). The overall severity of the outcome can further lead to detrimental

complications and increased mortality; thus, providing targeted interventions, ongoing education, and support to patients within the clinical setting will ensure positive outcomes (McKeaveney et al., 2020).

Collaborative bodies are created and endorsed to raise awareness and make recommendations for the safety of our patients. The International Immunosuppression and Transplant Skin Cancer Collaborative (ITSCC, 2025b), the British Association of Dermatologists (2024) and the British Society for Skin Care in Immunosuppressed Individuals (2025) all provide guidance, management and prevention strategies. They focus on all patients who have had a solid organ transplant and are on long-term immunosuppressive therapy. Clinically, it is recommended that patients be screened pre-transplant to determine any current skin lesions and potential precursors so that treatment can be determined if needed (Stasko & Hanlon, 2023). Furthermore, patients are expected to be continually assessed post-transplant in a post-transplant clinic, with the appropriate assessment tools being implemented to effectively educate and provide recommendations for the survival of their new kidney. The Renal Association (Baker et al., 2017) recommend in their guidance that skin cancer surveillance in post-transplant patients should be carried out twice a year for up to five years post-transplant and then annually post 5 years after transplant. Despite this, in 2020, a survey was conducted by Cordaro et al. (2020) to assess the current standards for transplant units in the skin assessment and monitoring of patients pre- and post-transplant. It was found that 33% of kidney units failed to screen patients post-kidney transplant, and if the patients were screened, it was not completed by a professional in the area (Cordaro et al., 2020). Despite the presence of a range of complexities in the assessment of skin cancer in renal transplant patients, regular screening protocols must be implemented within clinical areas, both pre- and post-transplant, to avoid potential harm to patients.

1.3 The research question

A Systematic Review (SR) was conducted to explore the evidence of a relationship between immunosuppression use and skin cancer. SRs are essential in research when exploring a topic that needs better understanding or highlighting gaps or

changes within practice. It is a method of gathering current published studies while having the skills to appraise, synthesise and refine the current evidence, further enhancing the research (Boland et al., 2023). SRs are structured and rigorous, assessing the quality of the current evidence whilst indicating potential gaps that may need a response, and reducing the risks of bias (Lame, 2019). For this SR, the PICO acronym was used to structure and define the research question. PICO: Population, Intervention, Comparison and Outcomes (Table 1) (Critical Appraisal Skills Programme [CASP], 2025c). Implementing this structured framework extracts all the crucial elements to support the research question (CASP, 2025d). Additionally, it guides the researcher during the eligibility process and remains consistent during the review process (Higgins & Green, n.d.).

Table 1: PICO

Population	Intervention	Comparison	Outcome
Adults with a history of a kidney transplant	Long-term immunosuppression use	Not applicable	An increased risk of developing skin cancer

Research question

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

In conclusion, it has been understood that there are risks directly associated with immunosuppression use and its potential link to skin cancer and this justifies the importance considering the adverse effects associated with the prolonged exposure to immunosuppressant medication post-kidney transplant. While the risks associated may not be prevented, the early detection and continuous monitoring of these patients will help them be treated more efficiently.

Having justified the topic and posed a research question, the research design will be outlined in the next chapter. It will begin with the aims and objectives, and a justification for the systematic review design. Chapter 3 will present the findings of the review as a narrative synthesis and these will be discussed in chapter 4. The

final chapter will conclude the dissertation with recommendations for practice and research.

Chapter 2: Research Design

2.1 Research Design

Chapter one identified the correlation between immunosuppression use and skin cancer risk in patients post-kidney transplantation. The relationship between these two variables has been established through previous quantitative research as seen in observational studies, non-randomised controlled trials, cohort studies and randomised controlled trials (RCTs). These studies aim to determine whether there is a positive or negative correlation. However, the exact relationship leading to the results depends on the methods used to collect the data and the quality of the research (Patel, 2009). The chosen research design guides the researcher in determining the type of research to be undertaken, while ultimately helping structure and plan the collection of necessary data for the particular piece of research (Sileyew, 2020; Khanday & Khanam, 2023). The aim of this study is to systematically review the existing literature to determine the association between the long-term use of immunosuppression medication and its direct link with skin cancer in adults (>18 years) post-kidney transplantation.

The primary objectives are:

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 included studies
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

While a primary research study would have been strong evidence, it was not deemed an appropriate design within the confines of a MSc project. Given the vast amount of evidence already existing, the ability to streamline and use an appropriate design is vital to produce accurate results, making the evidence accessible and

easily replicated in the future for further research (Khanday & Khanam, 2023; Lasserson et al., 2024). By refining and synthesising the latest established research, it was justified to conduct an SR of existing studies (Lame, 2019), which establishes and supports the credibility and robustness of the current evidence (CASP, 2025c). This SR has been aligned with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) framework (Page et al., 2021). This framework has been adhered to throughout the study process and is attached as Appendix 1. This framework helps researchers maintain transparency while adhering to rigour within the literature review structure. Specific tools can be employed to assess the quality of the research and reduce the risks of biases and limitations (Boland et al., 2023; Page et al., 2021).

SRs represent secondary research, while primary research provides original results by collecting new data to yield findings on a specific subject or question. Secondary research advances current knowledge through the amalgamation of multiple research sources to create a unified piece of work (Hofstra University, n.d; Lame, 2019). The hierarchy of evidence demonstrates that SRs are of the highest quality in research, indicated for use in numerous areas of healthcare to aid in developing current research (Wallace et al., 2022). Additionally, the benefits of undertaking secondary research, particularly for this piece of work, include the ability to analyse and explore the research topic in greater depth while reducing costs and potentially time when compared to primary research. The contribution to existing research provides a benchmark for further opportunities in endorsing the current leading research. Furthermore, it motivates ongoing exploration and potential future primary research to be completed after review. This may ultimately lead to further discoveries and continue to inform nursing practice with recommendations for the prevention and management of this patient group (Snyder, 2019).

As the posed research question, focuses on the relationship between two variables, immunosuppression and skin cancer, this situates the research within a positivist philosophy. Positivism focuses on exploration through science and statistics (Ali, 2024; Ghanad, 2023). The positivist paradigm emphasises the importance of interpreting the findings and their relevance to reality, thereby enhancing the credibility and robustness of the research (Park et al., 2020). Quantitative research

aligns with the positivist paradigm. Experimentation through non-randomised and randomised designs are the main drivers for studying larger population groups (Ali, 2024). This operates on the understanding that ‘it is what it is,’ without the influence of individual belief systems, which can be shown through qualitative data (Ali, 2024)..

RCTs are considered the gold standard within the hierarchy of scientific evidence and for clinical trials, which continue to enhance research validity and credibility (Boland et al., 2023; Higgins et al., 2019). It has, however, been acknowledged that RCTs may not be as credible within the hierarchy due to their broad applicability and generalisability. Non-randomised trials, such as cohort studies, are cheaper and less invasive in the methods used when attempting to prove an outcome from an exposure (Bosdriesz et al., 2020). Cochrane has acknowledged the use of non-randomised studies within SRs to be beneficial in the context of providing the evidence for the effects of longer-term outcomes and outcomes that may not be fully met by randomisation (Reeves et al., 2019). Cohort studies, in most cases, can assess an exposure and measure multiple outcomes related to this exposure, to create explanations for what is being studied, without the use of randomisation (de Vaus, 2001; Setia, 2016). This can be captured either retrospectively or prospectively. However, both these research designs come with their own strengths and limitations. They may differ in relation to whether the outcomes have either happened, through retrospective data, or not happened through prospective data (Wang & Kattan, 2020). Both study designs need careful consideration before implementation due to risks of bias, potential inaccuracies and lack of resources used due to restraints in time and requirements (Setia, 2016; Wang & Kattan, 2020). Higher-level observational study designs, recognised within the hierarchy of evidence, such as those through cohort studies, continue to achieve research validity comparable to RCTs. This is if each piece of work is carefully considered for potential flaws before concluding to a particular outcome (Setia, 2016; Wallace et al., 2022). Nevertheless, it continues to be well established that RCTs continue to offer a precise and rigorous design for data collection, which in turn leads to them still being considered as a valuable form of evidence that is consistently utilised within scientific research (Pearson et al., 2015).

Recent guidelines from NICE (2022) have identified the challenges proposed by the term ‘real-world evidence’ (RWE), which incorporates both quantitative and qualitative data in a more non-randomised control style. Challenges arise regarding the overall legitimacy of RWE in terms of various biases, trustworthiness, and the quality of the evidence (NICE, 2022). This form of research is estimated to improve clinical data and complement RCTs by enriching the evidence collected and creating a fuller picture (Dang, 2023). Cochrane encourages the use of non-randomised studies due to the differential outcomes compared to those of RCTs. They discuss how the complexities of including all outcomes from RCTs have been deemed difficult; therefore, there is a chance to redeem a more advanced range of findings within non-randomised studies (Higgins et al., 2024). While RCTs and non-randomised studies differ, they can support each other. Instead of relying solely on one particular form of study, for example, RCTs, could illustrate only a small portion of the research in that specific area of study (Bosdriesz et al., 2020; Bröckelmann et al., 2022). Both study types have their limitations. Multiple factors influence the quality and rigour of the research, making it crucial to assign appropriate tools to help mitigate the associated risks (Boland et al., 2023; Park et al., 2020). While the strengths and limitations of each study design need to be acknowledged to answer a research question appropriately (Wallace et al., 2022).

Establishing the validity and reliability of the studies enhances quality, while granting credibility so that other scholars and professionals reading the research can confidently implement it safely within practice (Heale & Twycross, 2015). To ensure the accuracy of the research, the inclusion of peer-reviewed papers is utilised. Peer-reviewed papers are well recognised not only for ensuring that the research is suitable for publication, but also to set standards which essentially avoid the publication of false information (Steer & Ernst, 2021). Despite this, there is still the potential for biases to occur during the research process. It is highlighted during the exploratory phase that there is a general demand for researchers wanting to prove something to be ‘right’ (Pacheco et al., 2023). However, this does not consider studies that may not necessarily validate this, which could lead to potential inaccuracies or underrepresentation of certain perspectives. Hence, the importance of two or more people exploring the matter (Pacheco et al., 2023; Wallace et al., 2022). Within this review, potential errors and biases will be taken into account and

identified. This is to avoid ambiguous information during the retrieval of the published work.

Isolating potential risks of bias during the retrieval process prompts the researcher to become critical about the piece of work being assessed during the eligibility process, while justifying its use and not obscuring the conclusion (Pannucci & Wilkins, 2010). To accomplish this, Cochrane developed and recommends the utilisation of the risk of bias tool (ROB2) for RCTs and the risk of bias in non-randomised studies of Interventions (ROBINS-I) for cohort studies (Cochrane Bias Methods Group, n.d; Cochrane Methods, n.d.). The ROB2 tool provides a framework to guide researchers on specific questions for RCTs to determine the overall risks of the findings. On the other hand, the ROBINS-I tool supports researchers in determining the overall effectiveness and risks of the findings; however, specifically associated with non-randomised studies (Sterne et al., 2016; Sterne et al., 2019). These tools were considered for implementation for each piece of research considered for the SR. That said, it was recognised during the review process that using both the ROB2 and ROBINS-I tools had been proven difficult to implement. Research by Crocker et al. (2023) supports the challenges that are faced during the implementation phase of the ROB tools, due to the complexities encountered. Both these tools assess the level of bias, whether at a low risk or high risk (Sterne, 2019). While the CASP tool is used to assess the quality of evidence, CASP (2025a) also acknowledges the sufficiency for recognising different types of bias. Therefore, utilising this tool to determine the validity and reliability of the findings was deemed appropriate.

Prior to undertaking the literature search, it is important to highlight the risk for bias that may be observed. Publication bias can result from research that may not have been published due to insignificant results, compared to other published studies identifying more substantial results (Song et al., 2013). This is reflected against the research question; however, while research eliminates potential unpublished work due to some inaccuracies within the results, it is still evident that this type of research continues to be considered as clinically significant within practice (Owens, 2021). Additionally, language bias would be carefully considered during screening due to the use of published work that has been written only in the English language. However, after a diligent review during pre-screening, it was considered that, due to

the inability to translate into other languages and the risk of a translation error and missed information, the use of English-language-only articles would be sufficient for use.

SRs do not involve human participants or primary research, as they utilise previously published documents that are readily accessible through relevant research databases. Therefore an ethical review is not required. It was, however confirmed by the Chair of the Research Ethics Committee (Appendix 2). This was completed before the undertaking of the SR to confirm that no risks would be involved. Despite an ethical review not being required, ethical principles still needed to be addressed and require disclosure due to potential issues that could still arise (Suri, 2020). It is important to remember that the process of an SR not only enables trust and respect but also helps researchers and readers alike get a better understanding of the topic under discussion. This then provides accuracy within the data and further validates research credibility and the current body of evidence (Bangdiwala, 2024).

Researchers should keep in mind the role of beneficence, which is to provide patient care that will overall be a benefit to them, but also to cause no harm. As professionals undertaking research, we have an obligation to the population to continue to provide effective care by carefully recognising benefits or risks that may be involved with participating in a specific study, whilst additionally respecting all participants' personal rights (Barrow et al., 2025; Varkey, 2021). Specifically within primary research, participants involved must be at minimal risk. However, within the context of secondary research, while there are no participants involved, the information gathered is crucial in providing the general public with the most favourable outcomes and results depending on the research being undertaken (Barrios et al., 2022). Beneficence is directly applied during the systematic process to avoid the use of information that has either not been appropriately appraised or that may raise concerns. These concerns involve risks of coercive behaviours or poor disclosures of the risks that may be involved during participation in the study (Barrow et al., 2025). Additionally, the risk of multiple search biases, including issues in the potential funding of some articles, may lead to the endorsement of publication. This can affect outcomes, leading to ethical implications that potentially affect decision-making processes (Suri, 2020). It is easy to overlook other aspects that can

affect outcomes, and that could be considered ethically challenging. Nevertheless, by acknowledging all the potential implications, in turn it helps to avoid incorporating them into future reviews. This enables professionals to make informed choices and provide effective clinical practice recommendations that have a positive effect on patient outcomes.

2.2 Search Strategy and Selection

In planning the search strategy, it is crucial to identify the broader and narrower terms to avoid missing essential search terms. This contributes to the reduction in the number of final papers retrieved for review. A primary search was performed on 12th March 2025 in the PubMed database to form standardised entry terms before finalising the full search alongside the use of Boolean operators. This was done using Medical Subject Headings (MeSH) (Table 2).

Table 2: MeSH standardised search terms

Population) “Renal Transplantation”, “Renal Transplantations”, “Kidney Transplantations”, “Kidney Grafting”
Intervention) “Immunosuppression Therapies”, “Immunosuppression Therapy”, “Immunosuppressive Therapy”, “Immunosuppressive Therapies”, “Immunosuppression”, “Immunotherapy”, “Immunosuppressive Agent”, Immunosuppressive Agents”
Comparison) Not applicable
Outcome) “Cutaneous Neoplasm” “Cutaneous Neoplasms”, “Skin Cancer”, Skin Cancers”, “Cutaneous Malignancy”, “Cutaneous Malignancies”, “Non-Melanoma skin cancer”, “Melanoma”

The Boolean Operators, ‘AND’ and ‘OR’, were used to help narrow down the search, while, simultaneously, truncation points have been included to help broaden the search by including the different word endings and/or spellings. The search terms and Boolean Operators used were: (Renal Transplant*) OR (Kidney transplant*) OR (Kidney Graft) OR (Renal graft) AND (Immunosuppress* therapy*) OR (Immunosuppression) OR (Immunotherapy) OR Immunosuppress* agents) AND

(Cutaneous neoplasm*) OR (Skin cancer*) OR (Cutaneous malignanc*) OR (Non-melanoma skin cancer) OR (Melanoma).

A rigorous literature search was conducted in the databases Medline, CINAHL and Embase. To track the search, a search ID was formed for each database to refine the results (Table 3-5). The tables identify the date of retrieval, the search terms used, the Boolean Operators, the action taken, the number of HITS and the limiters included alongside the number of final results. Bramer et al. (2017) found that for an optimal search, there are multiple databases that would need to be considered, including Embase, Medline and Google Scholar. The choice for the combination of Medline, Cinahl and Embase for this SR was based on the ability to index a range of RCTs and also research that has specialised components within the realm of medicine and nursing (Bramer et al., 2017; Lefebvre et al., 2025). Two further alternative databases were considered: the British Nursing Index and Nursing and Allied Health, both via ProQuest. However, after diligent review, it was considered that both these databases were highly reliant on qualitative research, case studies and literature reviews. Due to this SR being focused on quantitative RCTs and cohort studies, it was concluded that neither of these two databases would be sufficient in providing the further research for inclusion in the review. While it has been acknowledged that the inclusion of a few other databases is essential to be able to provide a satisfactory amount of references (Bramer et al., 2017), additional resources may be needed to have the ability to access any additional databases. This may be due to time restraints and consideration for only having one researcher undertaking the systematic process.

Table 3: Medline via EBSCOhost

Search	Date	Search options	Boolean operators	Actions	Results
S1	29/05/2025	(renal transplant*) OR (kidney transplant*) OR (kidney graft) OR (renal graft)	OR	View results	128,575
S2	29/05/2025	(immunosuppress* therap*) OR (immunosuppression) OR (immunotherapy) OR	OR	View results	402,858

		(immunosuppress* agents)			
S3	29/05/2025	(cutaneous neoplasm*) OR (skin cancer*) OR (cutaneous malignanc*) OR (non-melanoma skin cancer) OR (melanoma)	OR	View results	239,005
S4	29/05/2025		AND	View results	755
S5	29/05/2025	Limitors used: Publication Date: 2015/01/01-2025/12/31; English Language; Peer Reviewed; All adult: 19+ years; Medline only		View final results	157

Table 4: CINAHL via EBSCOhost

Search	Date	Search options	Boolean operators	Actions	Results
S1	29/05/2025	(renal transplant*) OR (kidney transplant*) OR (kidney graft) OR (renal graft)	OR	View results	17,076
S2	29/05/2025	(immunosuppress* therap*) OR (immunosuppression) OR (immunotherapy) OR (immunosuppress* agents)	OR	View results	52,873
S3	29/05/2025	(cutaneous neoplasm*) OR (skin cancer*) OR (cutaneous malignanc*) OR (non-melanoma skin cancer) OR (melanoma)	OR	View results	33,505
S4	29/05/2025		AND	View results	71
S5	29/05/2025	Limitors used: Publication Date: 2015/01/01-2025/12/31; English Language; Peer Reviewed; All adult; Exclude Medline records		View final results	6

Table 5: Embase

Search	Date	Search options	Boolean operators	Actions	Results
S1	26/06/2025	(renal transplant*) OR (kidney transplant*) OR	OR	View results	223,827

		(kidney graft) OR (renal graft)			
S2	26/06/2025	(immunosuppress* therap*) OR (immunosuppression) OR (immunotherapy) OR (immunosuppress* agents)	OR	View results	582,249
S3	26/06/2025	(cutaneous neoplasm*) OR (skin cancer*) OR (cutaneous malignanc*) OR (non-melanoma skin cancer) OR (melanoma)	OR	View results	326,290
S4	26/06/2025		AND	View results	1144
S5	26/06/2025	Limitors used: Publication Date: 2015/01/01-2025/12/31; English Language; Adult only		View final results	333

2.3 Data Reduction

After an extensive review of the literature, the results were filtered to reduce the amount of data collected before presenting the final findings. All studies initially had titles and abstracts screened for filtering purposes, and any acknowledged duplicates were removed. Records without an available abstract were screened based on the title, and if necessary, the full text was reviewed for relevance. Conference abstracts were initially evaluated based on the title and abstract; although they help minimise publication bias, they cannot be fully assessed and are not considered peer-reviewed (Hackenbroich et al., 2022; Scherer & Saldanha, 2019). This increases the resources and time required to extract information; therefore, conference abstracts were deemed unsuitable due to limitations in available time and resources and were removed during title and abstract screening. Any studies published in languages other than English and not excluded by the limiters were excluded manually during the full screening.

The full screening and selection criteria to omit the irrelevant research and incorporate those that are eligible have been identified in Table 6. This was

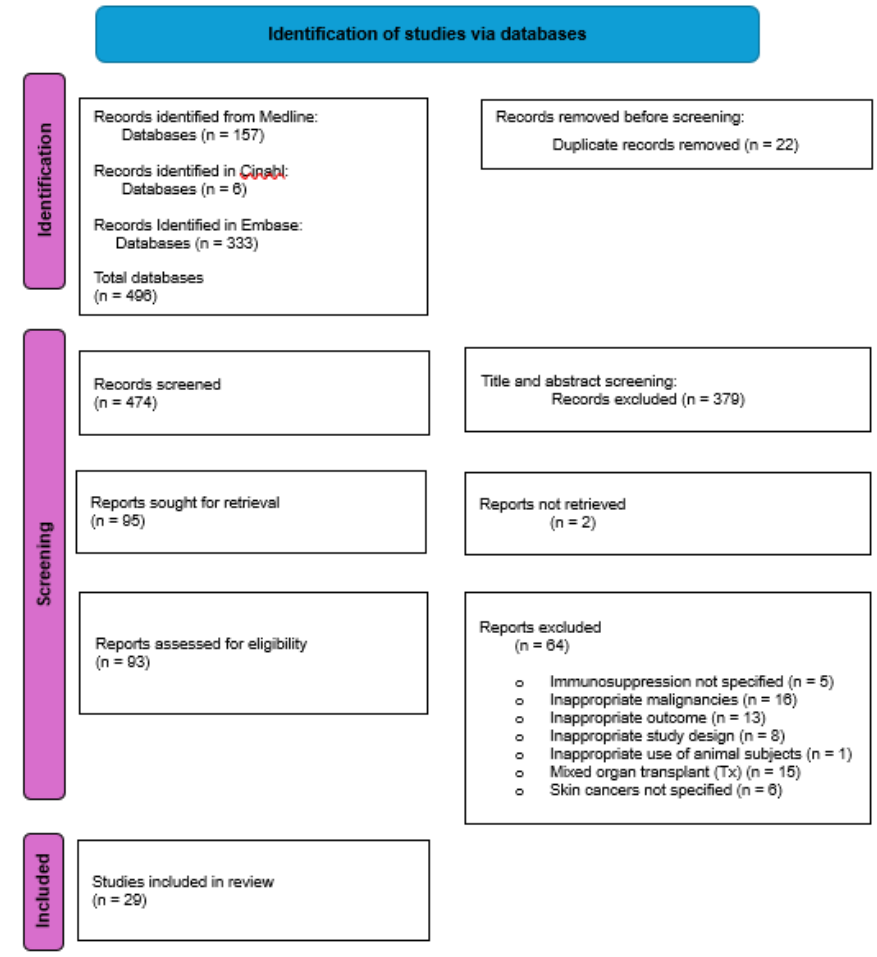
developed alongside the use of the PICOS tool and the research question. The components of the PICOS framework allowed for the development and clarification of the inclusion and exclusion criteria to be used. PICO also guided the selection and refinement of the research papers. A well-defined inclusion and exclusion criterion consists of the critical elements that are found within the research question and will help streamline the key components so that the review process is straightforward (Boland et al., 2023). The eligibility of the studies must meet the inclusion and exclusion criteria, which are provided consistently during the filtering and retrieval of articles and further reduces the potential risk of any implications. The review is limited to only primary research through engagement with RCTs, non-randomised trials such as cohort studies and observational studies. This is due to the potential for a more robust form of evidence which can complement one another when trying to answer the research question (Bröckelmann et al., 2022). During the assessment of the chosen studies' eligibility, the use of secondary sources could be included in the study, as applicable, through reference list searching (Owens, 2021). Additionally, any late exclusions should be noted later on in the search process when refining the criteria for review.

Table 6: Screening

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	. Policies . Reviews

	. Cohort studies	. 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

The PRISMA flow diagram (Figure 1) depicts the selection process. The initial phase identified the total number of papers before screening as 496, with Embase contributing the majority at 333, and CINAHL the fewest at 6. After the full screening process, including the application of inclusion and exclusion criteria, a total of 29 studies were included in this systematic review.



(Page et al., 2021)

Figure 1: PRISMA

2.4 Data Analysis and Presentation

Before presenting the selected studies and interpreting the significant findings, all relevant papers retrieved were observed for quality. The CASP tool for RCTs and cohort studies was utilised for this SR. This evidence-based tool is essential for evaluating research quality and rigour through a checklist that encompasses each type of study (CASP, n.d.). The CASP tool is appraised for its usage in qualitative studies (Long et al., 2020). However, there continues to be little evidence to support the use of this tool in appraising quantitative studies. Yet, results from an SR assessing the quality of multiple tools used for clinical studies do support the use of CASP as a tool for assessing RCTs (CASP, 2021; Zeng et al., 2015). Each research paper was thoroughly assessed for transparency and trustworthiness, thereby providing a rationale for the selection of studies. A completed CASP tool format utilising one of each of the studies for RCTs and cohort studies is included in Appendix 3. Additionally, a reduced format will be included in alphabetical order in Appendix 4 to ensure accessibility to the studies' overall score.

To support the quality of the evidence, the grade of recommendations assessment, development and evaluation (GRADE) approach was considered for this study. This framework has specifically been designed to examine and appraise the current evidence further supporting the use of recommendations for clinical practice (Schünemann et al., 2013). However, it is acknowledged that without sufficient training for the appropriate use, the terms for 'quality' and 'grading' of the research and the potential lack of reporting do impact the overall rating (Kolaski et al., 2023). As a result, this potentially distorts the review conclusion. Due to the time restraints for this SR and the lack of appropriate training, the use of the GRADE framework was acknowledged. However, the tool was deemed unfit for purpose due to the associated risks if used incorrectly. The use of the CASP tool is sufficient in analysing the quality of the studies and the risks of bias, to show any limitations within the current evidence on this particular topic.

Before synthesising the research, Higgins et al. (2019) recommend recognising the different patterns and features of the selected studies in a table. This supports

Cochrane's suggestion that presenting data in a table enhances transparency and helps the reader understand the review better, as it relies solely on the writer's interpretation (McKenzie & Brennan, 2019). Each selected study has findings displayed in a table following Cochrane's standardised format for the data collected (Schünemann et al., 2024a). The initial table of findings includes the author and study name, background, methodology, the number of participants, results, limitations, and the overall CASP score. A summary of this table is provided in Table 7.

Table 7: Example of the table of findings

Author and title of study	Background	Methodology	Participants	Results	Limitations	CASP score

While pooling the data in a meta-analysis could reduce subjectivity in interpretation of results and could improve the ability to determine correlation between the variables, to estimate the overall effect of immunosuppression on skin cancer risk (Higgins et al., 2024), a narrative synthesis approach was adopted. The findings are presented as a narrative synthesis. This form of synthesising helps inform the reader of common characteristics, whilst also acknowledging the relationships and patterns found (Randles & Finnegan, 2023). The synthesis is presented under common themes found within the research.

A narrative synthesis approach is recognised for use within SRs through the gathering of information to summarise further and interpret, leading to the understanding of how something can be correlated (Rai et al., 2020). According to a recent publication by the British Medical Journal [BMJ] (Campbell et al., 2018), it states that while the inclusion of a narrative synthesis introduces the potential risk for bias, it acknowledges how Cochrane supports the use of a narrative synthesis. Funded research is still ongoing by Cochrane to endorse the use of this synthesis within SRs (Thomson et al., 2018). While this would provide valuable insights into the research being conducted, it is important to note that whilst a narrative synthesis is sufficient in providing essential information needed to help answer the initial

research question, consideration has to be taken to avoid being overly simplistic in the description of the studies and their quality (Ryan, 2013).

While it could be hypothesised that there is a potential for the direct causation between the long-term use of immunosuppression and the increasing risks of skin cancer, it does not imply that immunosuppression is the direct cause of skin cancer (Gershman & Ullman, 2023). By synthesising the research data, the relationship between the variables may help identify potential corelation. However, there is a chance that other factors need to be considered beyond this specific study, as immunosuppression alone may only exert an ‘influence’ on the outcome (Barrowman, 2014). Consideration for geographical factors, skin type, age and sex are all important confounders that need to be acknowledged during the discussion phase, as these multiple factors can in turn affect the outcomes in the different patient groups that are being included in each study.

Having discussed the research design within this chapter, the following chapter will present the findings. The studies are presented in a table format, addressing the initial information while briefly describing study characteristics and the quality of each research paper and its risk of bias. From this, a more in-depth narrative synthesis is used to explore the themes between the studies and finally, the assessment of the study's strengths. The studies will be separated according to study type; for example, RCTs will be split from non-randomised control trials and cohort studies.

Chapter 3 Findings

This chapter focuses on the preliminary synthesis of the identified studies, aiming to answer the research question. Each study will be grouped separately; for example, RCTs are distinct from cohort studies and are then examined and briefly described within a table format. Providing a concise synthesis of the articles in a tabular format provides consistency within a narrative synthesis of the data and has been acknowledged by Cochrane for use within SRs (Ryan, 2013).

3.1 Screening

It is recommended that during multiple phases of the SR, the researcher reports what is deemed essential to screen current research efficiently, ensuring validity and the inclusion of high-quality studies (Page et al., 2021). The PRISMA (2020) checklist was used throughout this SR.

Twenty-nine papers were included for review. While the chosen studies had to meet the inclusion criteria for the best evidence, the attempt to include all potentially relevant articles is often difficult as it requires time and precision, regardless of the studies' validity and tendencies towards potential bias (Edinger & Cohen, 2013; Harvey & Dijkers, 2019). Edinger and Cohen (2013) report that within the review of papers, an effective systematic process should not only identify the essential papers needed for the review but also minimise the studies that need to be excluded. It is considered that, as an independent reviewer, there is an increased risk for missing potential studies during the exclusion process (Affengruber et al., 2022). The process by which systematic reviews are conducted is presented in a way that can highlight potential flaws and a risk for misleading and unreliable information being collected from the evidence (Kolaski et al., 2023). The CASP checklist is an acceptable tool for use within the systematic process when collecting evidence to establish the validity and quality of the results. Although it is recommended for use by novice researchers (Long et al., 2020), it is strongly advised that its use can be subjective, depending on the researcher and the skills and experience which they have acquired (Ma et al., 2020). In this review, the CASP checklists were utilised for all twenty-nine studies,

and they were assessed as either high, medium, or low quality. The CASP tool clarifies that, to determine validity and quality, the first three initial questions must be answered with a ‘yes’, allowing the researcher to proceed to the methodological order, with prompts guiding interpretation and response to these questions (CASP, 2021; CASP, 2024). Additionally, within the realm of quantitative research papers, it is important to appraise the use of statistical tests, with confidence intervals (CI) and p-values being used and drawn upon during the CASP appraisal process (Smith & Noble, 2025). However, research into the use of the CASP tool has questioned how these prompts might be interpreted differently by independent researchers and whether more focus on certain questions could lead to misinterpretation and affect applicability to the research paper (Long et al., 2020).

Whilst the CASP tool aims to validate each paper, Purssell (2020) highlights that it does not consider the entirety of the evidence, though the process of using the CASP tool can help to determine the outcomes of each paper and its overall credibility and relevance to the body of evidence under review (Purssell, 2020). Furthermore, Long et al. (2020) recognised that while the CASP tool is recommended, limited guidance exists on how it should be applied effectively during the review process, especially given the complexities involved (Purssell, 2020). This prompts researchers to question how to establish the validity of these papers formally. It is worth mentioning that alternative methods for validating papers using the CASP checklist have been explored, with a numerical scoring system representing answers to assess validity (Pluye et al., 2009). This approach allows for the setting of a threshold, although it is subjective and may increase the risks of inaccuracies and bias. Nonetheless, it continues to be recognised that this subjective interpretation continues to be employed by experienced researchers (Shrier et al., 2008). Consequently, overall outcomes should be interpreted and synthesised cautiously to minimise potential risks (Bauchner & Loannidis, 2024).

All full texts were thoroughly read, and reference lists were examined for relevance. This resulted in no additional studies being identified for inclusion during citation searching. However, during this screening process, a few articles were re-assessed for relevance, and it was considered that these papers generated substantial evidence for this SR. The reconsideration for the inclusion of these papers was

based on a personal choice to generate more robust evidence. The most common reasons for the inclusion of these potentially excluded studies are outlined below.

Inclusion reasons for potentially excluded articles

- Multiple organs were identified; however, the study used a separate analysis for renal transplant
- Multiple cancers were indentified; however, the study used separate analyses for skin cancer

3.2 Quality assessment

All studies included in this SR were assessed for quality and reliability. The CASP tool was deemed suitable in this SR for both RCTs and cohort studies. It is considered a useful tool for novice researchers because it is easier to understand, while having the potential to streamline questions, providing transparency in the review and supporting ongoing evidence (Long et al., 2020; Purssell, 2020). The CASP tool offers researchers with questions that appraise the studies, enabling a scoring system that highlights the paper's quality. An initial set of twelve questions for the CASP tool for cohort studies and eleven questions for the CASP tool for RCTs is divided into sections, guiding researchers through the systematic screening process (CASP, n.d.). Incorporating these questions allows researchers to systematically organise articles by quality and detect bias, ensuring that the work within the SR is accurate and trustworthy (Delavari et al., 2023). The tools’ main purpose is to assess the validity of the work, evaluate the overall results, and consider whether the research is applicable locally. The responses are recorded as either yes, no, or cannot tell. The response ‘cannot tell’ was used during the times that insufficient information was present to make an informal decision. Each answer was scored either a one for "yes" and a zero for "no" or "cannot tell" (Nadelson & Nadelson, 2014). It has been recognised that a higher score indicates the validity of the research (Olaghere et al., 2023), however while the quality rating is based on the number of ‘yes answers, it has been reported that if the first two or three questions do not provide a yes, then consideration and caution must be given to whether the

papers are credible and robust (CASP, 2023). Within this SR, each paper has been critically examined and scored to determine whether it is of high or low quality (Singh, 2013). This then helps to determine the overall validity of evidence presented (Kolaski et al., 2023).

3.3 Summary of Findings

The studies selected for this SR are presented in a tabulated form below (Tables 8 and 9). This method enhances ease for the reader to identify the key areas that can support and inform clinical practice (Fonnes & Rosenberg, 2025; Randles & Finnegan, 2023). The highest-scoring studies are presented first within the table, and progressively lower quality studies are listed further down. Additionally, the geographical area of each study has been recorded. The location of the study is important to consider, as outcomes can be influenced by the amount of UV exposure (Randles & Finnegan, 2023). The following accepted abbreviated key terms are consistent within nephrology and healthcare research (Jones-Hughes et al., 2016) and have been used within the table as follows: AZA (azathioprine), BAS (basiliximab), BCC (Basal cell carcinoma), CSA (ciclosporin), CNIs (calcineurin inhibitors), EVL (everolimus), GD (Glomerular disease), KS (Kaposi sarcoma), KTR (kidney transplant recipient), MMF (mycophenolate mofetil), MPA (mycophenolic acid), MPS (mycophenolate sodium), mTOR-i (mammalian target of rapamycin inhibitors), NMSC (non-melanoma skin cancers), SCC (Squamous cell carcinoma), SRL (sirolimus), TAC (tacrolimus), UV (ultraviolet) and UVA (Ultraviolet A radiation).

Table 8: Overview of results from cohort studies

Author and title of study	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
Shao et al. (2022) Higher mycophenolate dosage is associated with an increased risk of squamous cell carcinoma in kidney transplant recipients	The exploration of the immunosuppressive medication mycophenolate, as the sole medication use in KTRs and the risks to SCC and BCC	Prospective cohort study Located in Australia Recruitment over 19 months (November 2012 – June 2014)	134 KTRs Selected through a strict inclusion and exclusion criteria. Participants were enrolled from a previous study (Skin Tumours in Allograft Recipients; STAR)	No significant outcome between the use of MMF and BCC High MMF dose was shown for an increased risk of SCC The immunosuppressed individual for >5 years, showed an increased risk of SCC	Noted was the small number of participants in the study, however helped to provide a more extensive data collection due to close follow ups and a comprehensive data collection. Risk of generalisability bias, due to immunosuppression dose being particular for this hospital, however other hospital's may provide their patients other doses / regimens – to be considered	14/14

Opelz et al. (2016) Immunosuppression with mammalian target of rapamycin inhibitor and incidence of post-transplant cancer in kidney transplant recipients	The risks of de novo mTOR-i immunosuppression and patients not prescribed mTOR-i therapy and the direct link to cancer risks after KTRs	Retrospective analysis Located in Germany, but study focuses on multiple countries with use of an international registry Data collected from January 1999-December 2013 (14 years)	Total of 78,146 participants Selected using an inclusion and exclusion criteria and were registered with the collaborative transplant study (CTS) 73,867 without use of mTOR-i 4279 with use of mTOR-i	A reduced rate for the risks of NMSC in patients started on mTOR-i from the initial time post-transplant NMSC incidence lower in mTOR-i group Significant reduction was shown for BCC and there was no effect for SCC	Risks of missing data as relying on previous records from several years – however the use of an international registry strengthens external validity No information on the drug regimens – risks of missing information necessary for the final data	13/14
Thet et al. (2024) Comparison of skin cancer risk between renal transplant recipients and patients with glomerular diseases in rural Queensland	The incidence of skin cancers within the KTR on long term immunosuppression compared to that of Glomerular disease	Retrospective cohort Clinical data collected over 1 year Comparative observational Located in Queensland Australia	112 patients overall with either a kidney transplant or GD 65 eligible KTRs – 61 met inclusion criteria Reviewed in a clinic every 1-3 months	Immunosuppressive treatment is associated with increased risks of NMSC in KTRs First line induction therapy: • BAS Long term triple therapy: • CNI/ MMF and prednisolone Comparison to a study undertaken in Czech – Australia was x4 more times likely to get skin cancer – unsure as whether due to intensity of sun and/or UV index	Small sample size – may not be applicable to the wider population. Risk of underestimation Use of retrospective data on skin cancer exposure and immunosuppressant use – only confirmed via histology	13/14
Ducroux et al. (2017)	There is the awareness surrounding skin cancers post kidney transplants. However	Retrospective multicentric study	53 cases Patients selected through a strict	Of the 53 patients, a total of 958 epithelial skin tumours were diagnosed, with a total of 462 SCC	Small sample size and wide confidence intervals suggesting the need for a larger prospective study	12/14

Risk of aggressive skin cancers after kidney retransplantation in patients with previous posttransplant cutaneous squamous cell carcinomas: a retrospective study of 53 cases	little is known regarding the risks to patients after transplantation and in the longer term	Located in France and Netherlands Study split between six centres – 5 French and 1 Dutch Data collected over 14 months	inclusion and exclusion criteria. Patients must have had at least x1 SCC diagnosis after initial transplant. Inclusion of patients that have had their 2nd kidney transplant	There was a total of 4 patients with a new diagnosis of SCC post-transplant High dosage of CNI medication use linked to the reoccurrence The use of AZA over the two transplants was deemed a higher risk for development of SCC, so caution for this to be avoided Post transplant, 18 patients were prescribed mTOR-i Introducing mTOR-I reduced the risks of reoccurring SCC		
Fattouh et al. (2017) Increasing incidence of melanoma after solid organ transplantation: a retrospective epidemiological study	While the risks for NMSC are notably common in post-transplant patients, the risks for melanoma skin cancer is known to have limited data. This study indicates that the risks for melanoma in these patients are continuing to increase with poor outcomes.	Retrospective study Located in France Data collected over 24 years	1102 patients in kidney transplant cohort Selected only if they had skin carcinomas and melanoma	Within the 1102 patients, melanoma occurred within 6 patients The immunosuppression used is not directly noted for KTRs, however a majority were on a dual immunosuppression regimen at diagnosis of melanoma, including CNIs, AZA, CSA and MMF. It was concluded that the immunosuppression to be switched to a mTOR-I, due to the reduced risks and beneficial outcomes for melanoma	Risk of confounding bias due to no multivariable analysis Potential missing data - risk of over estimation or under estimation. 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	12/14

Shope et al. (2023) Characterizing skin cancer in transplant recipients by Fitzpatrick skin phototype	The incidence of skin cancers based of Fitzpatrick skin type and the influence of immunosuppression use	Retrospective cohort study Descriptive Located in South Carolina, USA Data collected over 10 years	Total of 163 KTRs Selection based on dermatological screening during the time for these patients	Total of 7 KTRs had post-transplant skin cancer Total of 156 KTRs did not develop post-transplant skin cancer Drug metabolite induced UVA photosensitivity with AZA CNIs causation for tumour development and mutation of potential cancer cells. Also increased UVA photosensitivity	Limited skin types (non-Asian or pacific were included) - risks of generalisability and external validity	12/14
Alves et al. (2024) Metastasis of skin squamous cell carcinoma in kidney transplant recipients	SCC is considered as one of the most common forms of skin cancers in KTRs due to the use of immunosuppression. It is essential that patient characteristics including clinical and histopathological, are determined, so to better understand the causes for the development of skin cancer metastasis.	Retrospective single centre study Located in Brazil Data collected between 2004-2021 (17 years)	Total of 29 patients split into two groups – 18 KTRs and 21 immunocompetent patients Selection of patients from a specific hospital in Brazil based on a strict inclusion and exclusion criteria	Immunosuppression use included 94.4% on CNIs, 55.6% on either AZA or MPS and 11.1% used mTOR-i The development of SCC in KTRs after 5 years post-transplant increased Average metastasis development was 11 months	Small sample size – risk of underestimation of effects No statistical analysis – risk of generatability and the inability to determine to association Risks of generalisability bias due to a single centre study	11/14
Ascha et al. (2017) Risk factors for melanoma in renal transplant recipients.	The risk factors and characteristics that are considered as a risk to KTRs that further progress to developing Melanomas. This is compared to the general population	Retrospective cohort study Located in Ohio, USA Patient data collected via a database and	105 174 KTRs within the database 488 went onto develop melanoma	CSA and SRL were both associated with the increased risk of melanoma in KTRs: • CSA p<.004 • SRL p<.001	There is a potential for the under reporting of the melanomas within database, as it has been acknowledged – risk of misclassification bias It was identified that not all cofounders were included e.g.	11/14

		over 8 years (2004-2012)		Need for optimal management of the immunosuppressive regimen used	Fitzpatrick scale and sun exposure, so potential for underestimation	
Fuhrmann et al. (2022) Cancer among kidney transplant recipients >20 years after transplantation: post-transplant lymphoproliferative disorder remains the most common cancer type in the ultra-long term	Long term survival of KTRs >20 years and cancer risk. Based on 10, 20 and 30 years post-transplant.	Retrospective cohort Observational Located in Switzerland Data collected over 18 years (1981-1999)	293 KTRs were studied out of 1241 Patients selected through a strict inclusion and exclusion criteria and medical records	145 (49.5%) KTRs developed NMSC 48 out of 74 (64.9%) already with cancer, developed NMSC NMSC rate of >60% after 30 years on immunosuppression	Limited to Caucasians and patients were known to have a higher rate of survival in Switzerland, compared to other regions globally – there potential risks of generalisability and external validity Single centre study – risk of generalisability bias and external validity There was the selection of participants that had survived an event of cancer post-transplant – this could lead to potential selection bias	11/14
Hayashida et al. (2015) Epidemiology and clinical evolution of non-melanoma skin cancer in renal transplant recipients: a single-centre experience in Sao Paulo, Brazil	Risks of NMSC in KTRs due to being immunocompromised over 5 years	Retrospective review Located in Brazil Data collected over 5 years (July 2004 - December 2009)	68 participants 55 patients used at least one cytotoxic drug: AZA, MPS and MMF 51 patients used a CNI (TAC and CSA) 2 patients used a mTOR-i (SRL) Participants selected based on medical records	Followed up over 3 years Invasive SCC – 139 tumours in 42 patients SCC – 103 tumours in 37 patients BCC – 101 tumours in 32 patients Early onset of NMSC was associate with TAC ($p < 0.001$) and MPS ($p < 0.003$) Higher incidence of NMSC in patients treated with CNI to immunosuppressive cytoxics	Small sample size – may not be broadly relevant to the wider population Retrospective analysis – risk of incomplete data.	11/14

Leonhard et al. (2023) Exhaustion of CD8+ central memory responder T cell differentiation provokes non-melanoma skin cancer in elderly kidney transplant recipients	The role immunity cells have in the body and their direct link with the development of NMSC. The choice of immunosuppression and the cancer causing properties or how it may reduce tumour growth	Observational study with comparison Located in Germany Patients followed up over a median of 2.1 years	133 KTRs participants without a history of NMSC (6 of these developed NMSC) 55 KTRs with a history of NMSC (49 patients post 2.0 years due to death & loss to follow up. Of these, 24 had reoccurrence)	Immunosuppressive therapy overall has an effect in relation to the immune cell changes, with it being discussed that immunosuppressive therapy influences on tumour promoting cells, causing a reduction in the ability to provide a cancer defending immune response Consideration for new immunosuppressive drugs to be considered as to prevent the imbalance	Study design – difficult to determine cause and effect because a 'snapshot' as only explores the risk. Need for clinical trial	11/14
Malagón-Liceaga et al. (2024) Skin cancer incidence in Mexican renal transplant recipients: a cohort over 56 years	This study is based over 56 years of data and looks at the incidence of skin cancers in KTRs alongside a cancer risk threshold of 10 years for use of immunosuppression and skin cancer risks	Retrospective cohort study Located in Mexico Data collected over 55 years and 8 months (August 1967 – April 2023)	1642 KTRs Patients were selected through electrical medical records based on strict inclusion criteria	Total of 385 malignant skin cancers were found in 108 KTRs MMF is noted to have a protective association against skin cancer (CI 0.2-0.6) CSA was a risk factor for skin cancer (CI: 1.8-5.5) The risks of NMSC, specifically SCC increased dramatically, specially the longer a patient was on immunosuppression Most profoundly at >30 years, whilst the risk of BCC dropped after 20-29 years	Single centre study - risks of generalisability bias Data collected over long period of time – risk to recall and selection bias Missing data including that of immunosuppression use and potential for incomplete data due to retrospective style – risks to misclassification as potentially missing values	11/14
Murray et al. (2020)	This study looks at KTRs and their risks to	Retrospective cohort study	4536 KTRs within the database found – a	Most common regime pre switch was:	Retrospective study – it was highlighted that there is a need to	11/14

The impact of switching to mTOR inhibitor-based immunosuppression on long-term non-melanoma skin cancer incidence and renal function in kidney and liver transplant recipients. NOTE: There were both KTRs and liver transplant patients studied, however there was a separate analysis for KTRs	developing NMSC, with SCC being recognised at the most intense regarding the development Immunosuppression is highlighted as one of the most troublesome issues in relation to the development of NMSC, however understanding how mTOR-i may reduce the incidence needs to be better understood	Located in the republic of Ireland Data was collected from KTRs between 1st January 1994 – 1st January 2015 (21 years)	total of 85 KTRs were included in the study (these patients met the criteria for the study which involved switching immunosuppressant from CNI to mTOR-i Patient selection: through the Irish national kidney program, meeting certain criteria	• CSA and AZA (44%) • TAC and MMF (33%). 42 out of 85 KTRs developed one NMSC 26 developed >2 NMSC 3 developed >5 NMSC Post switch regime: • SRL and MMF (60%) • SRL and AZA (19%) • SRL alone (21%). Post switch, 30 additionally NMSCs developed, yet only 4 KTRs went on to develop more than one NMSC	undertake a prospective study to assess further Small cohort of KTRs (85), may lead to poor statistical power against the general population Risk of generalisability as based in Ireland only, so unable to confirm it would be applicable externally	
Pinho et al. (2016) Non-melanoma skin cancer in Portuguese kidney transplant recipients-incidence and risk factors	Focused on the associated risks and the incidence of NMSC in KTRs within a Portuguese kidney transplant unit	Retrospective analysis Located in Portugal Data was collected from January 2004 – December 2013 (9 years)	288 KTRs Patient selection: purposively chosen if they were a KTR that was followed up in the 'Centro Hospitalar e Universitario de Coimbra' between the data collection dates	The total number of SCC diagnosed were 69 Total number of BCC diagnosed were 62 MMF was the most prescribed immunosuppressant, however presented the lowest risk to NMSC (<0.001) AZA had the highest risk of NMSC (p<0.01) In comparisons of all the immunosuppression regimens prescribed, regimen C (AZA and CSA)	Patients were included only if referred for a dermatological follow up – potential selection bias Information bias due to the only collection from clinical records, no database included	11/14

				had a x3.85 higher rate of NMSC		
Sachedina et al. (2024) Skin cancer in renal transplant recipients: outcomes from a safety net hospital in Boston.	The incidence and risk factors associated with KTRs and the development of skin cancer. This study also acknowledges patient skin colour and risks to skin cancer development, including the use of immunosuppression specifically in certain skin types	Retrospective cohort study Located in Boston Data collected from January 2000 – December 2022 (22 years)	777 total KTRs 245 were Fitzpatrick scale I-II 532 were Fitzpatrick scale III-VI Patient selection: based on a strict inclusion criterion within hospital medical records	52 out of 777 KTRs were diagnosed with skin cancer Fitzpatrick scale I-II: • 37 patients developed skin cancer (13 SCC, 12 BCC, 10 both SCC and BCC, 1 melanoma, SCC and BCC and 1 melanoma) Fitzpatrick scale III-VI: • 15 patients' developed skin cancer (8 SCC, 3 BCC, 1 both SCC and BCC, 3 KS Duration of immunosuppression >10 years shown to have a significant association SRL was the medication noted to have to higher risks for NMSC, however it was recognised that these patients were considered high risk patients and converted to SRL from CNI before diagnosis – multivariate analysis confirmed no significant risk	It has been noted that the risk factors associated with the increased risk of skin cancers and use of sirolimus, is due to confounding issues, therefore potential for confounding bias Single centre study – potential generalisability bias Data collected over long period of time – risk to recall and selection bias	11/14

Borlinić et al. (2017) Melanomas in renal transplant recipients: a single-centre study	Although deemed rarer, the risk of melanoma skin cancers is still recognised within renal transplant patients. This study reports the risks for the development of melanoma skin cancers within KTRs	Retrospective study Located in Croatia Data collected from 1973-2017 (44 years)	1889 KTRs Patient selection: from a patient database following strict inclusion criteria	Only 4 patients were diagnosed with melanoma: • 2 patients were on TAC, MMF and steroids • 1 was treated with CSA, AZA and steroids • 1 was treated with CSA, MMF and steroids	Potential bias for a low number of positive outcomes for the large study size. Not very generalisable. Missed factors include skin type, which could increase risks associated Risk of generalisability bias due to single centre study Data collected over long period of time – risk to recall and selection bias	10/14
Krásová et al. (2016) Immunosuppressive therapy in the post-transplant period and skin cancer	Risk of malignancies in KTRs with the use of immunosuppressive therapy, with skin cancer representing the commonest malignancy post-transplant	Retrospective prospective cohort study Located in Prague Data collected from KT between 1980-2016 (36 years) and	797 participants Patient selection: based on referral for a dermatological assessed between 2013-2016 and a strict inclusion criterion	Skin cancer in 63 patients (7.9%) NMSC most common with a total of 159 lesions noted in 61 patients: • BCC; 59.7% • SCC 30.8% The immunosuppression with statistical significance was identified as: • Group 1 on TAC, MMF and Cortisteroids • Group 3 on CSA, TAC, MMF and Cortisteroids	No cofounders noted and potential missing information, potentially leading to some inaccuracy or incomplete data Some indifferences in the number of participants between the different regimes – unable to detect statistical difference which is accounted for in the conclusion. Additionally, selection bias due to inconsistencies in numbers and the inability to present fair comparisons	10/14
Okut et al. (2017) Nonmelanoma skin cancers after kidney transplant: our 15 years of experience with mammalian target	KTRs whom developed NMSC post-transplant and the overall benefits in reducing immunosuppressive medication or switching the medication to	Retrospective study Located in Turkey Data collected from January	1016 medical records of patients reviewed 18 patients total were included	7 patients were diagnosed with SCC and 4 with BCC During the diagnostic period, the immunosuppressive regimen consisted of triple drug regimen including: • CNIs in 12 patients	Small sample size and non-randomised – potential selection bias Limited to one transplant centre retrospectively Limited detail into cancer type	10/14

of rapamycin inhibitors.	another form of immunosuppression	2000 – December 2014 (14 years)	Patient selection: assessed for inclusion based NMSC diagnosis post-transplant and a functional graft	• mTOR-i triple regimen in 3 patients • double drug regimen in 3 patients Post diagnosis, patients were switched to either a reduced dose double drug regimen or a single drug regimen The patients progressing with more NMSC were using a single based immunosuppressive drug The immunosuppression with the least risk was mTOR-i	Potential risk to confounding bias	
Musalem and Sáez-Vera (2025) Forty years of kidney transplantation: Insights into malignancies at a single center in Latin America	The risks of malignancy, including NMSCs and melanoma in post KTRs. Considering all multiple factors, will help to implement correct strategies into practice to prevent post-transplant malignancies	Retrospective analysis over 43 years and 6 months Located in Chile Data collected from January 1981 – July 2024	375 KTRs Patient selection: based on clinical records following a strict inclusion criterion	Primary immunosuppression agents were TAC and MMF NMSC formed 96% of the skin neoplasms Unable to fully detect direct harm from the use of immunosuppression, as unable to get blood results which prevented more accurate and precise results	Incomplete data - Unable to measure outcome of immunosuppression use through bloods – risk of measurement bias Risk of incomplete data from medical records Data collected over long period of time – risk to recall and selection bias	9/14
Bottomley et al. (2016) CD8+ immunosenescence predicts post-transplant cutaneous squamous cell	Compares the immunological markers used for SCC diagnosis in long term KTRs	Prospective, longitudinal cohort study Located in Oxford, United Kingdom	59 KTRs with history of post-transplant SCC 58 KTRs without history of SCC	522 days post enrolment, 28 participants developed a total of 57 SCC A history of pre study SCC increased the overall score of SCC development	Limited to Caucasians - risks of generalisability and external validity Few participants received induction therapy Newer immunosuppressants used, therefore unable to detect the effect on SCC	8/14

carcinoma in high-risk patients				Intensity and duration of immunosuppression use raise the risks of skin cancer alongside the use of steroids AZA could mutate cells, increasing the risks Most of the study participants were on CNIs: • KTRs with SCC pre study 49(83) • KTRs with no SCC pre study 47(81)		
Burke et al. (2015) Expression of Bcl-xL and Mcl-1 in the Nonmelanoma Skin Cancers of Renal Transplant Recipients	Addressed are the risks in patients on immunosuppression compared with patients who are not on immunosuppression in the development of skin cancers. This comparison determines the risks of these patients using immunosuppression and the influence it has on a group of proteins, that aims to protect the cells as to prevent the production of cancer cells 'apoptosis'	Retrospective observational study Located in Australia Data collected from September 2007 – October 2013 (6 years)	31 participants Patient selection based on convivence sampling through a database meeting inclusion criterion Divided into 3 study groups based on immunosuppression use: Sirolimus exposed (n=10); Tacrolimus exposed (n=11); No immunosuppression exposure (n=10)	Reduction of Bcl-xl in patients on immunosuppression TAC led to a reduced number of Mcl-1 cells compared to that of SRL – essential for cell survival. Potential for alternation of in the biology for the development of skin cancers	Sample sizes of both immunosuppression use groups similar, however overall, a small sample size – small statistical power, limited generalisability	8/14
Fázio et al. (2023) Use of sirolimus as an adjuvant therapy for kidney	KTRs are at high risk of SCC, specifically regarding certain immunosuppression use.	Prospective exploratory study. Non-randomised	44 KTRs 25 patients converted to SRL	Patients followed up over 36 months The conversion from CNI to SRL was shown to be	Single centre study – risk of generatability bias and external validity	8/14

transplant recipients with high-risk cutaneous squamous cell carcinomas: a prospective non-randomized controlled study.	This study explores whether converting patients to SRL from CNI medication will improve SCC prognosis. Most importantly would it help those patients already at high risk of SCC.	Located in Brazil Data collected between May 2015 – March 2018 (3 years)	19 patients kept on CNI Patient selected based on strict inclusion criteria: high risk SCC diagnosis on a continuous immunosuppression regime	effective, with a reduced rate of incidence in the high risk SCC patients	Small sample size – risk of publication bias due to the potential underreporting of effects Some patients refused conversion and a certain exclusion criterion for control group – risk of selection bias	
Cegielska et al. (2018) Evaluation of quantitative changes in regulatory T cells in peripheral blood of kidney transplant recipients with skin cancer after conversion to mTOR inhibitors	Skin cancer risks in patients on immunosuppression and the immune changes once initial immunosuppression use have been changed over to an alternative Comparisons for the use of mTOR-i immunosuppression in patients already within clinical diagnosis of skin cancer on previous immunosuppression include CNIs, AZA and MMF	Prospective cohort Located in Poland	14 patients converted to mTOR-i Control group includes 18 patients that had no changes made to their current immunosuppression regime	The incidence of skin cancer risks in patients on mTOR-i is generally considered a lower risk. Out of the 14 patients on the mTOR-i, only 1 skin neoplasm was detected, while 8 out of 18 patients on their originally immunosuppressant developed a skin neoplasm It was shown that the group with the mTOR-i, generally had an improved outcome compared to the control group	How the participants were recruited is not identified - Potential selection bias and risks to generalisability Confounding bias due to lack of randomisation	7/14
Crespo et al. (2017) Effector Antitumor and Regulatory T Cell Responses Influence the Development of Nonmelanoma Skin	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	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

Cancer in Kidney Transplant Patients			25 KTRs with SCC were on switched to EVL and reviewed after 1 year			
Sułowicz et al. (2017) Comparison of the incidence of skin cancers in patients on dialysis and after kidney transplantation	Comparison of the incidence of both the type of malignancy and risks associated with KTRs on immunosuppression Based on dermatological screening	Retrospective-prospective cohort study Comparative Located in Krakow, Poland	486 post-transplant participants from a deceased donor 60.9% men, 39.1% women	30/486 KTRs were diagnosed with skin cancer: • 25 NMSC (5.1%) - 18 BCC (3.7%) /10 SCC (2.1%) • 1 melanoma (0.2%) An additional 1 new skin cancer diagnosis appeared in 56% of KTRs with NMSC First diagnosis on NMSC was at a median of 74 months	Risk of confounding bias due to multiple differences including age, immunosuppression exposure and multiple other confounding	7/14

Table 9: Overview of results from RCTs

Author and title of study	Background	Methodology	Participants	Results	Limitations	CASP
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	Trial based linage study – outcomes of participants were incorporated alongside a data registry (ANZDATA) Using RCTs and prospective studies	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	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	9/11

	This study is a long term follow up of RCT participants	Located in Australia and New Zealand		Age was the greatest risk associated with the development of NMSC in patients on EVL		
Lim et al. (2017) The risk of cancer in kidney transplant recipients may be reduced in those maintained on everolimus and reduced cyclosporine.	This study looks at the risks associated with the use of EVL and a reduced exposure to CNI immunosuppression will have a reduced effect on the incidence on NMSC in KTRs	Initial study a prospective RCT – this is a long term follow up using RCT and registry data Located in Australia and New Zealand	95 KTRs 66 randomised to EVL 1.5mg or 3mg with reduced CSA 29 were on MPS and standard exposure to CSA	The patients randomised to EVL and a reduced exposure to CSA, had a lower risk for the development of cancer 17 (17.9%) developed NMSC Within the MPA group, the development of NMSC was up to 7 years post-transplant. A total of seven of the NMSC were SCC (39%)	Registry data may not consider all confounding factors, leading to potential confounding bias Unreported long term data in registry – risk of underestimation of outcomes Retention of EVL – 1.5mg (54.3%) and 3mg (54.8%) – potential missing data	8/11
Dantal et al. (2018) Sirolimus for secondary prevention of skin cancer in kidney transplant recipients: 5-year results	An extended 5 year study of the risk for KTRs and the skin cancers that occur. The study highlights the potential reduction of these skin cancers in patients on SRL as the chosen immunosuppressant, compared to patients on CNI immunosuppression	Randomised control trial Multicentre trials conducted in France	120 KTRs Assigned either to a SRL group (n=64) or a CNI group (n=56)	After 5 years post conversion of treatment to SRL, it was noted that patients had a reduced risk of developing any new SCC, compared to that in the CNI group. Total number of skin tumours during the protocol: • SRL group: 28/64 (43.7%%) with SCC and 13/64 (20.3%) with BCC, • CNI group: 45/56 (80.4%) with SCC and 21/56 (37.5%) with BCC Total number of skin tumours at complete follow up stage: • SRL group: 10/28 (35.7%) with SCC and 10/28 (35.7%) with BCC,	High levels of loss to follow up in both groups – risk of attrition bias. However, study does acknowledge dropouts within their work	7/11

				• CNI group: 14/25 (56%) with SCC and 10/25 (40%) with BCC Total number of new SCC: • SRL after at least three months of treatment = 14, • CNI group = 33 A total of three patients developed metastatic SCC whilst on CNI immunosuppressant		

The results from the selected papers have been filtered, with many of the studies employing a retrospective design (n=18). Five used a prospective approach, two employed a mixed retrospective-prospective approach, one was observational, and three were RCTs. The selected studies originated from multiple geographical areas, including Europe (n=13) (United Kingdom, Ireland, Spain, Poland, France, Germany, Croatia, Portugal, Switzerland, and Prague), Asia (n=1) (Turkey), North and South America (n=8) (South Carolina, Ohio, Boston, Chile, Brazil, Mexico), Australia and New Zealand (n=5), as well as from an international registry and multicentre study based in France.

To interpret these studies, a threshold was established to assess their quality. For cohort studies, fourteen questions were used; scores below 7 were considered low quality because at least half of the questions did not appropriately address valid outcomes, often due to bias or poor sampling techniques. Scores of 8-11 were regarded as medium quality, while scores of 12 or higher were classified as high quality. Based on these thresholds set for this review, sixteen of the cohort studies were rated as medium quality, seven rated as high quality, and three as low quality. In the context of the CASP checklist used for RCTs, there were eleven questions in total; one study scored nine, another scored eight, and a third scored seven. These three papers were noted overall as high-quality. Among the various studies, retrospective studies were most consistently used, while prospective studies and RCTs were less common. Using multiple retrospective and prospective studies allows researchers to generate real-world data that provides structure and applicability to the general population, provided the evidence sources are appropriate (Chodankar, 2021). Researchers should consider their objectives carefully, as retrospective studies alone cannot establish cause-and-effect relationships (Tofthagen, 2012). Therefore, it is necessary to incorporate multiple research designs to avoid bias and to combine existing data with new potential data. Although most of the evidence offers valuable context and insights, it is recommended that more prospective research be conducted.

3.4 Risk of bias

Throughout the studies, a certain level of risk from potential bias was judged. Recognising this flaw in the research is important to avoid overestimating or underestimating the results, which could affect external validity (Jahan et al., 2016). A summary of the main biases has been provided in the overview of results table above. It has been acknowledged that the risks of bias in these studies relate to limited external validity and the potential for poor generalisability. Many of the studies are retrospective and single-centred. While retrospective studies are valuable for considering multiple exposures and are cost-effective, they may lack integrity and introduce biases such as selection bias, attrition bias, and confounding bias (Kim et al., 2024). Several studies were limited to specific ethnicities, with variations in sample sizes; some studies had adequate samples, while others had smaller sample sizes. Additionally, data collection was considered incomplete in some of the studies due to limited resources. It is essential to acknowledge that RCTs were utilised to validate the research, since they are widely used and are considered crucial in providing accuracy and effective research that ensures applicability and reliable estimates (Braga et al., 2025). Yet, careful consideration has been given to potential factors that could cause the risk for a variety of biases in both non-randomised and randomised studies. It is important to remember that whilst these tools have been implemented to extract bias during the analysis of the research, it is not always possible to account for all bias (Sarri et al., 2022). However, these risks will be considered and explored more during the synthesis of the key findings in the discussion phase.

3.5 Synthesis of results

A narrative synthesis provides the review context and a structured synthesis of the literature results (Turnbull et al., 2023). Narrative synthesis facilitates identification of associations between data and other potential variables and confounders (Siddaway et al., 2019). Baumeister and Leary (1997) appraised the use of a narrative review within the literature in their framework and recognised its value in creating a systematic process that is rigorous and of high standard. By incorporating this type

of review, key components and common trends within the research are explored, with each topic organised under a subheading alongside a critical discussion (Randles & Finnegan, 2023). All studies were utilised during this phase, whether deemed high, medium or low quality. Though it has been acknowledged that using a narrative analysis can introduce risks of bias and a lack of transparency due to the interpretation of the work (Campbell et al., 2019). The potential for subjective interpretation may also increase bias, as the researcher's personal views and biases can influence the review process, potentially affecting the interpretation of the data collected (Shrier et al., 2008). It could be argued that, while the risk of subjective interpretation rises with narrative synthesis, subjectivity is inherently present during the systematic process, highlighting the necessity for general caution (Uttley et al., 2023). Therefore, it is considered acceptable to use other methods within an SR and during the synthesis of results (Cumpston et al., 2023). It is important to acknowledge that, although this SR will not statistically synthesise results, it is essential to understand the papers' p-values and confidence intervals (CI). The interpretation of the evidence requires an understanding of its significance and strengths rather than relying solely on the conclusions (Shreffler & Huecker, 2023). Schünemann et al. (2024b) describe these values, where CIs define a range reflecting the 'true effect', with a wider interval indicating uncertainty, while a narrower interval suggests greater certainty. The precision of these estimates depends on multiple factors, including the size of the study. Meanwhile, p-values help determine whether the data are statistically significant, typically with a threshold of <0.05 indicating significance (Schünemann et al., 2024b).

In the following chapter, the evidence extracted is compiled together under subheadings to summaries the main findings. These will be discussed and critically reviewed to identify the core elements drawn from the studies to answer the research question. All commonalities and discrepancies will collectively generate a substantial body of evidence for exploration. The papers' characteristics are formulated to withstand critique, whilst being supported by other literature. While the low-quality studies are not fully omitted from the study, the research would be best incorporated within the following discussion phase. This was completed with caution, to enable the discussion for bias in more depth, whilst also extracting potential evidence that may be suitable for discussion.

Chapter 4: Discussion

This chapter focuses on a discussion of findings. The complexities of the association between immunosuppression use and skin cancer risk will be discussed, with potential limitations drawn from the research design and execution.

4.1 Discussion

It is a requirement for the long-term use of immunosuppression in post-transplant recipients to reduce the risk of rejection and improve patient survival rates (NICE, 2017). Evidence suggests that the ‘gold standard’ immunosuppressive treatments include the use of CNIs, m-TOR inhibitors, antiproliferatives, glucocorticoids, and biological immunosuppressive agents (Szumilas et al., 2023). In light of this, the research has supported the use of a triple therapy regimen as maintenance in KTRs involving the use of a CNI, alongside an antiproliferative agent and corticosteroids (Cheung et al., 2022). Yet, NICE (2017) guidance has not officially been able to make recommendations regarding the ongoing use of this combination and its safety aspects. Despite this, varied regimes are being utilised within practice, which are patient dependent (Szumilas et al., 2023). Depending on the optimisation of these medications and the monitoring of patients, associated risks become apparent. This further leads to other adverse outcomes such as graft issues, toxicity and immunological risks, alongside long-term complications, including cancers (Bamoulid et al., 2015; Wojciechowski & Wiseman, 2021).

In order to synthesise and evaluate the results, the studies have been mapped out and summarised under subheadings. This follows a narrative analysis structure, which provides the appropriate information in relation to the subject being researched. It has often been employed in quantitative research that has multiple factors and relationships that may further influence a specific outcome (Siddaway et al., 2019). Five main headings are identified, reflecting the challenges associated with the use of immunosuppression and the cause of skin cancer development.

4.1.1. Risks of NMSC vs Melanoma

The research identifies skin cancers to be considerably higher in KTRs than in any other organ transplant recipients (Shope et al., 2023). Yet in comparison to other research, the overall risk of skin cancer generally applies to all major solid organ transplants (Wheless et al., 2022). KTRs remain highly predisposed to NMSC due to long-term immunosuppressive treatment (Hennawy et al., 2025). Twenty-six of the twenty-nine studies focused on NMSC, while ten included data on melanoma risks either separately or alongside NMSC risks. The notable difference between NMSC and melanoma has highlighted, with Shope et al. (2023) noting that 75.86% of patients developed NMSC, compared to 3.45% with melanoma. This has been supported by more recent research from Musalem and Sáez-Vera (2025), who acknowledged that NMSC accounts for 96% of all diagnosed neoplasms. Although the risk of developing multiple NMSCs in KTRs is well established, SCC is emphasised as the most significant (Hayashida et al., 2015). One study by Kaufmann et al. (2016) reported a 3.3 times higher likelihood of developing SCC compared to BCC. However, in contrast to this, various researchers still suggest that BCC is considered the more recognisable NMSC (Krasova et al., 2016; Sulowicz et al., 2017), while the overall prevalence of melanoma remains relatively low at around 0.2% of KTRs (Borlinić et al., 2017). A subsequent study reported that the risk of both BCC and SCC is significantly higher than that of melanoma. The literature has suggested that BCC tends to be diagnosed first, while SCC may be diagnosed a few years later, although developing more rapidly (Granata et al., 2023). The association between incidence, particularly of SCC and BCC, varies depending on geographical area (Pinho et al., 2016), with Australia being identified as having the highest risk and southern Europe and Italy the lowest risk (Granata et al., 2023). The overall prevalence of NMSCs also increases dramatically after the age of 80 (Fuhrmann et al., 2022). That being said, there is increased significance in patients 40 years and over showing a higher risk of NMSC diagnosis, with the average age being around 51 years (Hayashida et al., 2015). Additionally, the development of NMSC in patients aged 60 and above has been documented to occur within a shorter time frame of around 3-5 years post-transplant (Granata et al., 2023).

The increased recognition of both NMSC and melanoma risks over longer periods is logical, given that more successful grafts last longer, which in turn leads to extended periods of immunosuppression, consequently increasing the patients' age and other systemic factors (Kaufmann et al., 2016). However, increasing age can be correlated with a shorter duration of immunosuppression use, due to increased mortality (Fattouh et al., 2017). Long-term transplant survivors with successful grafts belong to a specific population whose risk for other comorbidities rises significantly, alongside the risks for other associated infections and cancer incidences (Krenzien et al., 2015). Considering this, both the duration and dosage of immunosuppression become more relevant in this patient group, alongside other factors such as advancing age, patient demographics, skin types, and external influences (Burke et al., 2015; Fattouh et al., 2017; Hayashida et al., 2015).

4.1.2. Duration of immunosuppression

A common feature in the studies is the focus on the duration of immunosuppression use and the increased risk of skin cancers. Fifteen studies examine the risk associated with the length of immunosuppression, ranging from one to thirty years, for the development of skin cancer. It is clear that the longer the duration of immunosuppression and the older the patients are, the higher the overall hazard risk (Ascha et al., 2017). Lim et al. (2017) found that depending on the patients' prescribed immunosuppression, the risks for developing skin cancer occurred anywhere between 1 year and 7 years post-transplant. A more recent study by Thet et al. (2024) discussed the incidence of NMSCs at 1 year, 3 years, and 5 years of immunosuppressant use, while additionally identifying a significant increase from the 3-year mark. Fuhrmann et al. (2022) amplify this scope, recognising the proportion of NMSC at 10, 20, and 30 years, with 30 years showing a significant rise in NMSC occurrence after kidney transplantation.

One particular study's multivariable analysis of potential factors affecting NMSC incidence shows that, during the first 20 years post-transplant and immunosuppression use, NMSC risk increases notably with age and the duration of immunosuppression, and, in particular, the development of SCC and the use of a

high mycophenolate dose (Kaufmann et al., 2016; Shao et al., 2022). However, other research has either demonstrated that MMF can show resilience towards skin cancer (Malagón-Liceaga et al., 2024), while the theory for the duration of immunosuppression to be a good indicator for SCC alone lacks substance (Bottomley et al., 2016). The duration of immunosuppression and the risks for melanoma specifically were shown on average to occur at around 9.8 years (Fattouh et al., 2017). While it has been perceived that melanoma risks are significant, they do not compare to the risks associated with developing NMSC over prolonged exposure to immunosuppression (Malagón-Liceaga et al., 2024). Despite this, existing literature supports the risks for development of melanomas in KTRs, specifically associated with immunosuppression duration and cellular changes (Granata et al., 2023). However, MM usually start as benign growths or slow changes within the skin's cells (Granata et al., 2023). Furthermore, it has been discussed that the risks in patients undergoing their second transplantation include an increased development of aggressive SCC, which may be linked to extended immunosuppression, as observed by Ducroux et al. (2017). It is important to highlight the type of immunosuppression used and the specific duration, as this can support time frames for the development of skin cancer, with varied distributions being documented for the first NMSC development and diagnosis (Kaufmann et al., 2016; Okut et al., 2017).

4.1.3. CNI medication, antibotoblites and triple therapy treatments

The absolute risk of developing NMSC increases by 27.9% from pre-kidney transplant to post-transplant (Thet et al., 2024). Considerable evidence suggests that the use of CNI, mycophenolate, and azathioprine in particular shows a significant association with tumour formation and skin cancer (Kaufmann et al., 2016; Shao et al., 2022). While the number and strength of immunosuppressants used do not always imply an increased risk of NMSC, single-use immunosuppressants may have the potential to increase these risks alone (Sachedina et al., 2024). However, the research indicates that it is the combination of these medications that is often used, suggesting the overall treatment regimen rather than individual immunosuppressants being associated with the overall risk (Ducroux et al., 2017). A recent study

undertaken by Alves et al. (2024) indicates a strong correlation between the use of individual immunosuppression in their patients and their chances of developing SCC, specifically with metastasis. The correlation between SCC development and metastasis is reflected in a study by Malagón-Liceaga et al. (2024), with it being suggested that SCC was responsible for 85.7% of metastasis developed.

While several predictors are linked to immunosuppression use alone, the inclusion of a corticosteroid is also common during therapy (Fattouh et al., 2017). It is understood that all triple therapy regimens include the use of a steroid, which has also been associated with an increased risk of skin cancer (Bottomley et al., 2016). Ducroux et al. (2017) highlight that 9.4% of their patients developed an aggressive form of SCC after the initial transplant while on corticosteroids and azathioprine or in combination with an additional immunosuppressant such as cyclosporine. The safety profile for reducing or eliminating steroids during triple therapy is not always recommended due to the risks related to rejection rates; therefore, low-dose steroid treatment or weaning off steroids is more likely advised, depending on the patient and immunosuppression regimen (Cheung & Tang, 2022; Ekberg et al., 2025).

Lim et al. (2017) study utilised RCTs and registry data, showing the increased development of NMSC up to approximately 7 years post-transplant within patients who were taking mycophenolate sodium, compared to those on everolimus. Shao et al. (2022) support this by specifically highlighting the use of the cytotoxic drug mycophenolate at high dosage as a contributing factor. However, Malagón-Liceaga et al. (2024) best describe mycophenolate as a low risk compared to that of cyclosporine and azathioprine. External sources also determine the low risk for the use of mycophenolate and the total risk for the development of NMSC (Mittal & Colegio, 2017). Yet it continues to be used as an option for triple therapy treatment. While the associated risks have been deemed low, a more recently established study has emphasised that there is limited research on the overall malignancy risk, specifically with the use of MMF (Scott et al., 2022). While caution is needed, the utilisation of mycophenolate at increased dosage has been mentioned in our research to be associated with the particular development of SCC (Shao et al., 2022). This therefore supports the theory that the specific treatment regimen, dosage, and duration of treatment may be detrimental factors for the development of

NMSCs, rather than individual immunosuppressive medications (Mittal & Colegio, 2017; Rollan et al., 2022).

Multiple pieces of research over the years have not shied away from claiming that the particular use of azathioprine can increase the likelihood that KTRs will develop some form of NMSC (Kreuz et al., 2025; Maddox & Soltani, 2008; Malagón-Liceaga et al., 2024; Pinho et al., 2016). In this review, the use of azathioprine was found to significantly increase the risk of NMSC (2.85 OR, $p < 0.01$), whilst patients on a specific regimen including azathioprine and cyclosporine had a 3.85 times higher risk (3.84 OR, $p = 0.01$) (Pinho et al., 2016). The long-term safety aspects for the use of azathioprine indicate the increased risks of skin cancers (DrugBank, n.d.). Yet in terms of efficacy and when compared with mycophenolate, azathioprine is generally the less preferred choice for effectiveness or is acknowledged as a slightly outdated choice for immunosuppression, as seen in both our research and alternative studies (Pinho et al., 2016; Ruggenenti et al., 2021; Struckmeier et al., 2024). In contrast, while the use of cyclosporine has been recognised as a risk factor for the development of NMSC (Malagón-Liceaga et al., 2024), the dosage alone continues to play a major role in the development of NMSC (Dantal et al., 2018; Lim et al., 2017).

CNIs continue to be used within most triple therapy regimens; however, the research has considered the benefits for the use of this immunosuppression in combination with an mTOR-i such as everolimus (Lim et al., 2017). It has also been observed that whether a routine dose or reduced dose is provided, CNIs continue to exhibit carcinogenic changes leading to increased risk for NMSC development (Dantal et al., 2018). It is understood that patients who are at risk of graft rejection often receive an increased requirement of immunosuppressive treatment, therefore influencing the overall risk factor for the development of skin cancer (Musalem & Sáez-Vera, 2025). Therefore, the reduction of certain immunosuppression treatments may, in fact, reduce the risk of NMSC by nearly, if not more than, half (Ying et al., 2018). While this is true, this comes at an additional cost. By reducing immunosuppressive therapy, other risks become more prevalent, causing an increased risk for graft rejection. Maintenance immunosuppression therapy continues to regularly consist of triple therapy, including a CNI medication, antimetabolite and steroids (Fuhrmann et

al., 2022). Depending on the KTRs or the clinical area, the choice of immunosuppressive treatment and the intensity may vary. There is a tendency for clinical areas to favour certain immunosuppressants due to their positive effects, affordability, and the potential for lowering rejection rates post-transplant (Musalem & Sáez-Vera, 2025; Ruggenenti et al., 2021). Yet, there continues to be diligence for the use of specific immunosuppressants, with evidence indicating the replacement over time by an alternative immunosuppressant, such as that of mTOR-i (Murray et al., 2020; Sachedina et al., 2024). This in turn suggests the possibility of increased risks for the use of certain medications alone (Ducroux et al., 2017).

4.1.4 Shifting treatment to the use of mTOR-i

Thirteen research papers specifically explored the use of mTOR-i as an alternative immunosuppressant that could potentially support kidney function, with recent suggestions indicating that this choice might lower the risk of developing skin cancer (Ducroux et al., 2017; Murray et al., 2020). Retrospective data collected by Murray et al. (2020) and Sachedina et al. (2024) indicate that switching immunosuppressive treatment to sirolimus may be associated with lower risks and protective factors, showing a reduction rate for NMSC of approximately 50%. Whereas one of the sirolimus derivatives, everolimus (Kajiwara & Masuda, 2016), was shown to have no benefit in relation to the reduction of NMSC when used as an isolated treatment option (Ying et al., 2018). Contrary to earlier findings, it has been reported that the association between the use of sirolimus and the development of NMSC has been reported on previously. It has been identified that there were no protective factors for the development of NMSC associated with the use of sirolimus as an initial treatment (Pinho et al., 2016). However, the conversion to sirolimus has shown beneficial outcomes as opposed to the use of other immunosuppressant regimes. It has been reported that while NMSC has been diagnosed in patients on sirolimus, patients who were converted to sirolimus had a greater probability for a diagnosis of skin-related cancers while being on CNI, or a reduced development of NMSCs post-switch (Murray et al., 2020; Sachedina et al., 2024). Ying et al. (2018) examined the incidence of cancer and its long-term outcomes between the use of CNIs alone (tacrolimus or cyclosporine) with MMF or MPA, or a conversion to everolimus with

either a reduced dose of CNI (RD-CNI) or CNI withdrawal (CNI-WD). Results showed statistical significance favouring everolimus and RD-CNI, with a reduction in the development of NMSC (95% confidence interval 0.30-1.12, p=.1). Although there was no significant reduction observed with CNI-WD (95% CI 0.49-2.57, p=.8). Supporting this, Lim et al. (2017) compared two dosages of everolimus- 1.5mg and 3mg-. It was shown that whilst both dosages lowered the risk of NMSC in this patient group, the 3mg dose was associated with relatively better outcomes (95% CI 0.04-0.74) (Lim et al., 2017).

It was recognised that the effects of mTOR-i may generally only correlate with a significant reduction in BCC, compared to that of SCC (Dantal et al., 2018; Opelz et al., 2016). Fázio et al. (2023) explored the conversion to sirolimus in patients already diagnosed with cSCC. It was generally well-tolerated and showed a positive correlation with a reduced number of skin lesions during treatment, compared to that of patients taking CNIs (Fázio et al., 2023). Crespo et al. (2017) enhance this perspective by acknowledging the relapse rate as being significantly higher in CNI SCC than that of mTOR-i SCC. Conversely, Burke et al. (2015) observed that, while taking mTOR-i, a diagnosis of SCC was associated with a reduced level of tumour thickness compared to those taking CNI. This review continued to recognise a positive correlation between the conversion of immunosuppressants for the choice of mTOR-I. However, careful consideration is still needed for other potential outcomes, as the likelihood for graft rejection increases during the phase of immunosuppressant reduction or conversion (Okut et al., 2017). Similarly, the concern for the use of mTOR-i and the effects it has on mortality and potential graft dysfunction from conversion is generally recognised (Struckmeier et al., 2024). Whilst other associated factors, including age, specifically that of >50 years, were shown to be positively associated with the development of NMSC whilst taking everolimus (Ying et al., 2018). This is subject to different interpretations, as other confounding and patient-dependent factors always need to be considered. Yet, generally, the switch from the use of CNIs and antimotabilites to the use of mTOR-i following potentially poor outcomes continues to be validated (Ducroux et al., 2017; Lim et al., 2017). The use of mTOR-i has shown a high degree of stability, alongside a reduction of up to 56% in the rates for the development of NMSCs generally (Dantal et al., 2018; Lim et al., 2017; Ying et al., 2018). Additionally, other research

supports the use of low-dose CNI immunosuppression alongside an mTOR-I for its potential to reduce the risk of drug-related toxicity associated with high CNI immunosuppression concentrations (Kajiwara & Masuda, 2016).

4.1.5 The immune system and cell response

During the search phase of this review, several articles discussed the effects of immunosuppression on the immune system. It was shown that the responses that lead to immunological changes can be detrimental and ultimately contribute to the formation of skin cancer cells (Crespo et al., 2017). A total of five out of twenty-nine studies examined these responses. It was recognised that the initiation of immunosuppressive treatment significantly influences certain cell activation processes, resulting in systemic inflammation and accumulation (Leonhard et al., 2023). Age has an impact on the overall risk, with a general decline systemically, alongside a declining immune function due to increased age (Krenzien et al., 2015). While immunosuppression clearly has systemic effects to sustain the transplanted organ, the specific immunosuppressive impact may vary depending on the immunosuppressant used and the particular cells that the medication targets (Hussain & Khan, 2022). However, complexities can occur when identifying how the medication impacts the immune system in the cases of skin cancer development. This is due to the different regimens these patients are prescribed (Euvrard et al., 2004). The findings seemed to acknowledge that the switch of immunosuppression for the use of MMF has protective effects that offset any negative effects (Bottomley et al., 2016). Moreover, the cellular changes associated with the use of different immunosuppressants have been noted to exhibit similarities, indicating that there are no outstanding risks related to one another (Burke et al., 2015). However, all cellular changes impact cells within the epidermis, and the choice of immunosuppression can be a potential indicator of whether these changes are reduced or amplified (Burke et al., 2015). The understanding of how immunosuppression affects these particular cells is still not well understood. This highlights the potential lack of evidence surrounding this. More research is needed into the use of immunosuppressive medications and how they target particular cells that lead to the development of skin cancer (Leonhard et al., 2023).

4.2 Strengths and limitations

In the twenty-nine reviewed studies, substantial evidence pointed to a significant association between the use of immunosuppression and the significant implications for risk, specifically skin cancer. However, recognised within both the selected research papers and other collaborative groups (International Transplant Skin Cancer Collaborative, 2025a; Szumilas et al., 2023), it is not without its limitations. Overall, the search strategy was straightforward to implement, and the use of the PICO tool aided in defining the search terms. This facilitated a comprehensive search across all relevant databases. The overall evidence was considered moderate. Completing the SR as an independent researcher, could be viewed as a limitation in itself due to potential risks of subjective interpretation (Uttley et al., 2023). Involving dual researchers to execute the rigorous review process is recommended (Stoll et al., 2019). Therefore, any future SR should aim to involve multiple researchers to reduce the increased risks of bias and errors (Owens, 2021). Many research papers presented varied data concerning the duration of data collection, with some collecting data for over 20 years (Malagón-Liceaga et al., 2024). This offers substantial contextual information on the overall incidence of skin cancer within the population and aids in identifying long-term patient outcomes. However, it is important to recognise that sun habits have changed over time, alongside shifts in medication use and alterations in the ozone layer, which in turn have increased UV exposure (Parker, 2020). Additionally, a few studies identified an extended data collection period and the reliance on medical records, which could lead to missing data, potentially causing the final results to be over- or underestimated and introducing recall bias (Alves et al., 2024; Borlinić et al., 2017; Fattouh et al., 2017; Malagón-Liceaga et al., 2024; Musalem & Sáez-Vera, 2025; Sachedina et al., 2024; Thet et al., 2024). Nevertheless, the utilisation of international registry data strengthened some studies' validity, making them valuable during discussions and reducing the risk of bias related to generalisability and validity. Despite potential limitations, the systematic process adhered to the appropriate guidelines, notably, the PRISMA (2020) checklist (Page et al., 2021;

Uttley et al., 2023). Most studies were retrospective in design, and whilst these are vital for gathering previous data on the detrimental impact of long-term immunosuppression on KTRs, there remains a need for more prospective cohort studies and RCTs. This judgement is supported by the research, as smaller sample sizes and wider confidence intervals were observed, indicating the necessity for larger prospective studies (Ducroux et al., 2017; Hayashida et al., 2015; Murray et al., 2020).

The purpose of this research was to determine the potential correlation between immunosuppression use and skin cancer risks. While both prospective studies and RCTs are often well supported within retrospective data for future research (Wang & Kattan, 2020), retrospective studies provided essential knowledge regarding the associated risks and will guide future investigations. Practitioners should tailor their regimes according to local guidance while continuing to be aware of the implications on patients and how treatment should be individualised.

Having discussed the findings in this chapter and considered the limitations to the research design, overall conclusions and recommendations for practice are considered in the next chapter.

Chapter 5: Conclusion & Recommendations

5.1 Conclusion

The narrative synthesis methods used for this SR are subject to scrutiny regarding their reliability and suitability for synthesising the quantitative data (Campbell et al., 2019). More advanced methods for quantitative synthesis include the use of statistical analysis and meta-analysis. Due to the time restrictions of an assessed dissertation project and the resources available, this influenced how effectively these methods could be applied, resulting in the use of simpler methods (Higgins et al., 2019). It is beneficial for SRs to be completed by multiple researchers, given the expertise required to implement complex methods (Owens, 2021). Whilst the narrative synthesis may not be as precise as undertaking a statistical synthesis through meta-analysis, it still has the capacity to provide this SR with a rich collection of evidence that establishes the necessary background in answer to the research question (Higgins et al., 2019).

The findings of this SR are consistent, indicating that immunosuppression in KTRs is linked with a higher risk of skin cancer development. Yet, the likelihood that immunosuppression is recognised as a causal factor influencing skin cancer lacks sufficient validation. It may be more appropriate to acknowledge the link as a correlating variable. However, it is important to mention that whilst this review provides substantial information regarding correlating variables, the outcomes do not allow for definitive conclusions. Based on the research findings, researchers continue to have a better understanding of multiple variables that are detrimental to the development of skin cancers. However, there continues to be an emphasis on the use of long-term immunosuppression. It may be suggested that immunosuppression can act independently, whilst it may predominantly work in conjunction with other factors and variables, which in turn influence the outcome and severity. Multiple variables are considered during patient assessment, as other confounding factors influence the overall outcome and risks for these patients (Higgins et al., 2019). During the research, various factors were recognised to contribute to the heightened risks, including confounding and predisposing factors

such as UV exposure, geographical location, Fitzpatrick scale, ethnicity, gender, age, duration and dosage of immunosuppression, and individual cellular changes (Granata et al., 2023; Karlsson et al., 2021). Nevertheless, understanding what specifically increases this risk remains challenging, as the process is acknowledged to be complex (Rollan et al., 2022) with both extrinsic and intrinsic factors affecting patients' risks.

In summary, the current research indicates that adjusting immunosuppression can lead to better patient outcomes. It was widely acknowledged that azathioprine was recognised as one of the most harmful immunosuppressive drugs due to its photosensitising properties. In comparison, mycophenolate was linked to an increased incidence of SCC, particularly in some studies. Supplementary to this, the use of steroids and the increased risks of skin cancer were briefly mentioned. From the research, it was difficult to determine whether steroid usage increased the risk, as it tended to be used alongside immunosuppression during triple therapy treatment. However, it was the switching of immunosuppressive treatment from a triple therapy regimen involving a CNI immunosuppressant and steroid, to an mTOR-i, that was shown to have benefits in the reduced rates of skin cancer. This was recognised especially over the longer term. Leading on from this, NMSCs were generally the predominant type of skin cancer found in this patient group compared to melanomas, although it remained unclear whether the development of NMSC was solely related to an increased risk of BCC or SCC. Nevertheless, SCC appeared to be the most frequently observed skin cancer lesion after immunosuppressive therapy, with BCCs being the second most common (Hayashida et al., 2015). Additionally, SCC was suggested to be the most detrimental in the risks for metastasis, in comparison to that of BCC and MM (Malagón-Liceaga et al., 2024).

The research suggests that although many individual immunosuppressive medications have adverse side effects associated with long- term use, their dosage should be carefully monitored and reduced when appropriate to lower associated risks (Bottomley, 2016). Care must be taken to prevent other risks related to medication adjustments, including the risk of rejection. Therefore, tailoring immunosuppressive therapy to individual patients is vital, whilst considering personal factors such as age, sex, and gender. Additionally, the effects that different forms of

immunosuppression have at a cellular level and how they influence and shape different cellular pathways have been reported on. However, more research is needed, particularly on the impact that these immunosuppressive regimens have on cellular changes and tumour responses.

The research question asked whether there is an association between long-term immunosuppressive therapy and skin cancer risk in kidney transplant recipients. The research question was answered to some extent. However, it cannot be fully established whether immunosuppression is a direct cause of skin cancer. Whilst this SR may become a valuable piece of evidence, supporting ongoing research, it does highlight the need for the inclusion of larger prospective studies. It was acknowledged during the screening process that some articles were excluded due to being formatted in another language. This is important to consider, as with most research, having the inclusion of multiple articles globally is important to factor in different geographical areas. Through this SR, it has been identified that different regions globally have different sun habits and UV exposures, which in turn affect patient outcomes. The inclusion of data from multiple regions ensures the research has broad and comprehensive evidence (Walpole, 2019). However, the inclusion of all articles is not always achievable due to the resources available. The assessment and evaluation of the studies were completed appropriately using tools recommended by Cochrane. However, some tools, while being relevant when appraising the research, were difficult to incorporate. The decision not to incorporate certain tools during this SR was justified during the screening phase. Any future research would consider the incorporation of these additional tools alongside a multi-researcher approach for the reduced risks of bias and enhancing the transparency and reliability of the research.

5.2 Recommendations

1. Ongoing research is indicated in areas associated with the use of immunosuppression, specifically for larger studies, more prospective research, confirmatory studies and RCTs. Nevertheless, this SR has provided background and context of the research, which in turn assists healthcare

professionals in finding the necessary information and the right tools to help guide safe and professional practice (Walpole, 2019).

2. Researchers and non-researchers alike must continue to consider all contributing factors and variables that will affect KTRs in the long term. Additionally, it is necessary to acknowledge other forms of research that are available to provide ongoing future research with more comprehensive and precise information (Scherer & Saldanha, 2019).
3. Given the increasing incidence of skin cancers in this patient group, healthcare providers must monitor post-KTRs regularly and integrate the appropriate surveillance and screening tools into post-transplant clinics to help inform future improvements.
4. Clinical practitioners should continue to consider how to best improve clinical outcomes and how to achieve them, which may include the revision of patients' immunosuppressive regimens. However, practitioners should incorporate best guidance and gold-standard evidence into their standard working practice, with their practice being reflective of ongoing research.
5. Finally, the appropriate referral pathways and independent policies should be established early on within clinical practice to continue to ensure safe working practices for all healthcare providers.

References

Affengruber, L., Dobrescu, A., Persad, E., Klerings, I., Wagner, G., Sommer, I., & Gartlehner, G. (2022). Characteristics and recovery methods of studies falsely excluded during literature screening: A systematic review. *Systematic Reviews, 11*, 236. https://doi.org/10.1186/s13643-022-02109-w

Ahn, E., & Kang, H. (2018). Introduction to systematic review and meta-analysis. *Korean Journal of Anesthesiology, 71*(2), 103–112. https://doi.org/10.4097/kjae.2018.71.2.103

Ali, I. M. (2024). A guide for positivist research paradigm: From philosophy to methodology. *Idealogy Journal, 9*(2). https://doi.org/10.24191/idealogy.v9i2.596

Alves, F. F., de Jesus, L. C., Cristelli, M. P., Enokihara, M. M. E. S., Hirata, S. H., Facina, A. D. S., & Tomimori, J. (2024). Metastasis of skin squamous cell carcinoma in kidney transplant recipients. *International Journal of Dermatology, 63*(5), 560–564. https://doi.org/10.1111/ijd.17029

Ascha, M., Ascha, M. S., Tanenbaum, J., & Bordeaux, J. S. (2017). Risk factors for melanoma in renal transplant recipients. *JAMA Dermatology, 153*(11), 1130–1136. https://doi.org/10.1001/jamadermatol.2017.2291

Baker, R. J., Mark, P. B., Patel, R. K., Stevens, K. K., & Palmer, N. (2017). *Post-operative care in the kidney transplant recipient: Renal Association clinical practice guideline* [PDF]. Renal Association. https://www.ukkidney.org/sites/default/files/FINAL-Post-Operative-Care-Guideline-1.pdf

Bamoulid, J., Staeck, O., Halleck, F., Khadzhynov, D., Brakemeier, S., Dürr, M., & Budde, K. (2015). The need for minimization strategies: Current problems of immunosuppression. *Transplant International, 28*(8), 891–900. https://doi.org/10.1111/tri.12553

Bangdiwala, S. I. (2024). The importance of systematic reviews. *International Journal of Injury Control and Safety Promotion, 31*(3), 347–349. https://doi.org/10.1080/17457300.2024.2388484

Barker, C. F., & Markmann, J. F. (2013). Historical overview of transplantation. *Cold Spring Harbor Perspectives in Medicine, 3*(4), a014977. https://doi.org/10.1101/cshperspect.a014977

Barrios, L. M., Levy, G. A. M., Díaz-Anzaldúa, A., & Camarena, E. E. (2022). Rethinking benefits in health research: Reflections of an ethics committee. *Yale Journal of Biology and Medicine, 95*(3), 389–398.

Barrow, J. M., Brannan, G. D., & Khandhar, P. B. (2025). Research ethics. In *StatPearls*. StatPearls Publishing. https://www.ncbi.nlm.nih.gov/books/NBK459281/

Barrowman, N. (2014). Correlation, causation, and confusion. *The New Atlantis, 43*, 23–44.

Bauchner, H., & Loannidis, J. P. A. (2024). The subjective interpretation of the medical evidence. *JAMA Health Forum, 5*(3), e240213. https://doi.org/10.1001/jamahealthforum.2024.0213

Baumeister, R. F., & Leary, M. R. (1997). Writing narrative literature reviews. *Review of General Psychology, 1*(3), 311–320. https://doi.org/10.1037/1089-2680.1.3.311

Boland, A., Cherry, M. G., & Dickson, R. (2023). *Doing a systematic review: A student's guide* (2nd ed.). SAGE Publications.

Bolognia, J. L., Schaffer, J. V., & Cerroni, L. **(Eds.).** (2016). *Dermatology* (4th ed.). Elsevier.

Borlinić, T., Knežević, T., Gellineo, L., Franceschi, M., Bukvić Mokos, Z., & Bašić-Jukić, N. (2017). Melanomas in renal transplant recipients: A single-centre study. *Acta Dermatovenerologica Croatica, 25*(4), 281.

Bosdriesz, J. R., Stel, V. S., van Diepen, M., Meuleman, Y., Dekker, F. W., Zoccali, C., & Jager, K. J. (2020). Evidence-based medicine: When observational studies are better than randomized controlled trials. *Nephrology, 25*(10), 737–743. https://doi.org/10.1111/nep.13742

Bottomley, M. J., Harden, P. N., & Wood, K. J. (2016). CD8+ immunosenescence predicts post-transplant cutaneous squamous cell carcinoma in high-risk patients. *Journal of the American Society of Nephrology, 27*(5), 1505–1515. https://doi.org/10.1681/ASN.2015030250

Braga, L. H., Farrokhyar, F., Dönmez, M. İ., Nelson, C. P., Haid, B., Herbst, K., Garriboli, M., Cascio, S., Nieuwhof-Leppink, A., Kaefer, M., Bagli, J. D., Kalfa, N., Ching, C., Fossum, M., & Harper, L. (2025). Randomized controlled trials: The what, when, how and why. *Journal of Pediatric Urology, 21*(2), 397–404. https://doi.org/10.1016/j.jpurol.2024.11.021

Bramer, W. M., Giustini, D., Kramer, B. M., & Anderson, P. F. (2013). The comparative recall of Google Scholar versus PubMed in identical searches for biomedical systematic reviews: A review of searches used in systematic reviews. *Systematic Reviews, 2*(1), 115. https://doi.org/10.1186/2046-4053-2-115

Bramer, W. M., Rethlefsen, M. L., Kleijnen, J., & Franco, O. H. (2017). Optimal database combinations for literature searches in systematic reviews: A prospective exploratory study. *Systematic Reviews, 6*(1), 245. https://doi.org/10.1186/s13643-017-0644-y

British Association of Dermatologists. (2024). *Skin cancer advice for organ transplant recipients*. https://www.bad.org.uk/pils/skin-cancer-advice-for-organ-transplant-recipients/

British Society for Skin Care in Immunosuppressed Individuals. (2025). *Home*. https://www.bsscii.org.uk/

Bröckelmann, N., Balduzzi, S., Harms, L., Beyerbach, J., Petropoulou, M., Kubiak, C., Wolkewitz, M., Meerpohl, J. J., & Schwingshackl, L. (2022). Evaluating

agreement between bodies of evidence from randomized controlled trials and cohort studies in medical research: A meta-epidemiological study. *BMC Medicine, 20*(1), 174. https://doi.org/10.1186/s12916-022-02369-2

Burke, M. T., Morais, C., Oliver, K. A., Lambie, D. L., Gobe, G. C., Carroll, R. P., Staatz, C. E., Sinnya, S., Soyer, H. P., Winterford, C., Haass, N. K., Campbell, S. B., & Isbel, N. M. (2015). Expression of Bcl-xL and Mcl-1 in the nonmelanoma skin cancers of renal transplant recipients. *American Journal of Clinical Pathology, 143*(4), 514–526. https://doi.org/10.1309/AJCPQNB5WA3PLQBK

Campbell, M., Katikireddi, S. V., Sowden, A., & Thomson, H. (2019). Lack of transparency in reporting narrative synthesis of quantitative data: A methodological assessment of systematic reviews. *Journal of Clinical Epidemiology, 105*, 1–9. https://doi.org/10.1016/j.jclinepi.2018.08.019

Campbell, M., Katikireddi, S. V., Sowden, A., Thomson, H., & Sanderson, E. (2018). Improving conduct and reporting of narrative synthesis of quantitative data (ICONS-Quant): Protocol for a mixed methods study to develop a reporting guideline. *BMJ Open, 8*(2), e020064. https://doi.org/10.1136/bmjopen-2017-020064

Cancer Research UK. (2022). *Non-melanoma skin cancer statistics*. https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/non-melanoma-skin-cancer

Cancer Research UK. (2023a). *Melanoma skin cancer incidence statistics*. https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/melanoma-skin-cancer/incidence

Cancer Research UK. (2023b). *Skin cancer risks and causes*. https://www.cancerresearchuk.org/about-cancer/skin-cancer/risks-causes

Cancer Research UK. (n.d.). *Which treatments are used for Kaposi's sarcoma?* https://www.cancerresearchuk.org/about-cancer/soft-tissue-sarcoma/types/which-treatments-are-used-for-kaposis-sarcoma

Cegielska, A., Lisowska, K., Dębska-Ślizień, A., Imko-Walczuk, B., Okuniewska, A., & Rutkowski, B. (2018). Evaluation of quantitative changes in regulatory T cells in peripheral blood of kidney transplant recipients with skin cancer after conversion to mTOR inhibitors. *Postępy Dermatologii i Alergologii, 35*(5), 474–480. https://doi.org/10.5114/ada.2018.77237

Cheung, C. Y., & Tang, S. C. W. (2022). Personalized immunosuppression after kidney transplantation. *Nephrology, 27*(6), 475–483. https://doi.org/10.1111/nep.14035

Chien, L. Y. (2019). Evidence-based practice and nursing research. *The Journal of Nursing Research, 27*(4), e29. https://doi.org/10.1097/jnr.0000000000000346

Chodankar, D. (2021). Introduction to real-world evidence studies. *Perspectives in Clinical Research, 12*(3), 171–174. https://doi.org/10.4103/picr.picr_62_21

Cochrane Bias Methods Group. (n.d.). *RoB 2: Revised Cochrane risk-of-bias tool for randomized trials*. Cochrane. https://methods.cochrane.org/bias/resources/rob-2-revised-cochrane-risk-bias-tool-randomized-trials

Cochrane Methods. (n.d.). *ROBINS-I tool*. https://methods.cochrane.org/robins-i

Cordaro, A., Dobbs, T. D., Gibson, J. A., Whitaker, S., & Whitaker, I. S. (2020). Skin cancer screening in organ transplant centres in the United Kingdom: A national survey. *European Journal of Dermatology, 30*(4), 372–376. https://doi.org/10.1684/ejd.2020.3793

Crespo, E., Fernandez, L., Lúcia, M., Melilli, E., Lauzurica, R., Penin, R. M., Quer, A., Luque, S., Quero, M., Manonelles, A., Torras, J., Cruzado, J. M., Canas, L., Grinyo, J. M., & Bestard, O. (2017). Effector antitumor and

regulatory T cell responses influence the development of nonmelanoma skin cancer in kidney transplant patients. *Transplantation, 101*(9), 2102–2110. https://doi.org/10.1097/TP.0000000000001759

Critical Appraisal Skills Programme. (2021). *CASP randomised controlled trial checklist* [PDF]. https://casp-uk.net/checklists-archive/casp-rct-randomised-controlled-trial-checklist.pdf

Critical Appraisal Skills Programme. (2023). *How do I score my answers when using a CASP checklist?* https://casp-uk.net/faqs/

Critical Appraisal Skills Programme. (2024). *CASP cohort study checklist*. https://casp-uk.net/casp-tools-checklists/

Critical Appraisal Skills Programme. (2025a). *Different types of research bias*. https://casp-uk.net/news/different-types-of-research-bias/

Critical Appraisal Skills Programme. (2025b). *How to use the PICO framework to aid critical appraisal*. https://casp-uk.net/pico-framework/

Critical Appraisal Skills Programme. (2025c). *Systematic review vs meta-analysis*. https://casp-uk.net/news/systematic-review-vs-meta-analysis/

Critical Appraisal Skills Programme. (n.d.). *How to use our CASP checklists*. https://casp-uk.net/how-to-use-checklist/

Crocker, T. F., Lam, N., Jordao, M., Brundle, C., Prescott, M., Forster, A., Ensor, J., Gladman, J., & Clegg, A. (2023). Risk-of-bias assessment using Cochrane's revised tool for randomized trials (RoB 2) was useful but challenging and resource-intensive: Observations from a systematic review. *Journal of Clinical Epidemiology, 161*, 39–45. https://doi.org/10.1016/j.jclinepi.2023.06.015

Cumpston, M. S., Brennan, S. E., Ryan, R., & McKenzie, J. E. (2023). Synthesis methods other than meta-analysis were commonly used but seldom

specified: Survey of systematic reviews. *Journal of Clinical Epidemiology, 156*, 42–52. https://doi.org/10.1016/j.jclinepi.2023.02.003

Dang, A. (2023). Real-world evidence: A primer. *Pharmaceutical Medicine, 37*(1), 25–36. https://doi.org/10.1007/s40290-022-00456-6

Dantal, J., Morelon, E., Rostaing, L., Goffin, E., Brocard, A., Tromme, I., Broeders, N., del Marmol, V., Chatelet, V., Dompmartin, A., Kessler, M., Serra, A., Hofbauer, G. F. L., Kamar, N., Pouteil-Noble, C., Kanitakis, J., Roux, A., Decullier, E., Euvrard, S., & TUMORAPA Study Group. (2018). Sirolimus for secondary prevention of skin cancer in kidney transplant recipients: 5-year results. *Journal of Clinical Oncology, 36*(25), 2612–2620. https://doi.org/10.1200/JCO.2017.76.6691

De Pasquale, C., Veroux, M., Indelicato, L., Sinagra, N., Giaquinta, A., Fornaro, M., Veroux, P., & Pistorio, M. L. (2014). Psychopathological aspects of kidney transplantation: Efficacy of a multidisciplinary team. *World Journal of Transplantation, 4*(4), 267. https://doi.org/10.5500/wjt.v4.i4.267

de Vaus, D. A. (2001). *Research design in social research*. SAGE Publications.

Delavari, S., Pourahmadi, M., & Barzkar, F. (2023). What quality assessment tool should I use? A practical guide for systematic reviews authors. *Iranian Journal of Medical Sciences, 48*(3), 229–231. https://doi.org/10.30476/IJMS.2023.98401.3038

DrugBank. (n.d.). *Azathioprine (DB00993)*. https://go.drugbank.com/drugs/DB00993

Ducroux, E., Martin, C., Bavinck, J. N. B., Decullier, E., Brocard, A., Westhuis-van Elsäcker, M. E., Lebbe, C., Frances, C., Morelon, E., Legendre, C., Joly, P., Kanitakis, J., Jullien, D., Euvrard, S., & Dantal, J. (2017). Risk of aggressive skin cancers after kidney retransplantation in patients with previous posttransplant cutaneous squamous cell carcinomas: A retrospective study of 53 cases. *Transplantation, 101*(4), e133–e141. https://doi.org/10.1097/TP.0000000000001644

Edinger, T., & Cohen, A. M. (2013). A large-scale analysis of the reasons given for excluding articles that are retrieved by literature search during systematic review. In *AMIA Annual Symposium Proceedings* (Vol. 2013, p. 379).

Ekberg, J., Enevoldsen, A. E. A., Wallquist, C., Skov, K., Jespersen, B., Lindnér, P., & Baid-Agrawal, S. (2025). Steroid avoidance with low-dose tacrolimus is safe and effective in the long term for kidney transplant recipients. *Kidney International Reports.* https://doi.org/10.1016/j.ekir.2025.06.016

Euvrard, S., Ulrich, C., & Lefrançois, N. (2004). Immunosuppressants and skin cancer in transplant patients: Focus on rapamycin. *Dermatologic Surgery, 30*(4 Pt 2), 628–633.

Fallahzadeh, M. K., Khan, S., Zibari, G. B., Patil, S., & Singh, N. (2014). Local graft irradiation for kidney allograft rejection: A case series and review of the literature. *Nephro-Urology Monthly, 6*(3), e16262. https://doi.org/10.5812/numonthly.16262

Fattouh, K., Ducroux, E., Decullier, E., Kanitakis, J., Morelon, E., Boissonnat, P., Sebbag, L., Jullien, D., & Euvrard, S. (2017). Increasing incidence of melanoma after solid organ transplantation: A retrospective epidemiological study. *Transplant International, 30*(11), 1172–1180. https://doi.org/10.1111/tri.13011

Fázio, M. R. D., Cristelli, M. P., Tomimori, J., Koga, C. E., Ogawa, M. M., Beneventi, G. T., Tedesco-Silva, H., & Medina-Pestana, J. (2023). Use of sirolimus as an adjuvant therapy for kidney transplant recipients with high-risk cutaneous squamous cell carcinomas: A prospective non-randomized controlled study. *Brazilian Journal of Nephrology, 45*, 480–487. https://doi.org/10.1590/2175-8239-JBN-2023-0013en

Fonnes, S., & Rosenberg, J. (2025). Researcher's guide for the preparation of tables. *Journal of Surgical Research, 310*, 209–217. https://doi.org/10.1016/j.jss.2025.03.034

Fuhrmann, J. D., Valkova, K., von Moos, S., Wüthrich, R. P., Müller, T. F., & Schachtner, T. (2022). Cancer among kidney transplant recipients >20 years after transplantation: Post-transplant lymphoproliferative disorder remains the most common cancer type in the ultra long term. *Clinical Kidney Journal, 15*(6), 1152–1159. https://doi.org/10.1093/ckj/sfac013

Gershman, S. J., & Ullman, T. D. (2023). Causal implicatures from correlational statements. *PLOS ONE, 18*(5), e0286067. https://doi.org/10.1371/journal.pone.0286067

Ghanad, A. (2023). An overview of quantitative research methods. *International Journal of Multidisciplinary Research and Analysis, 6*(8), 3794–3803. https://doi.org/10.47191/ijmra/v6-i8-52

Government of Jersey. (2024a). *Channel Islands cancer incidence and mortality report 2007 to 2020.*https://www.gov.je/SiteCollectionDocuments/Health%20and%20wellbeing/Channel%20Islands%20report%202007%20to%202020.pdf

Government of Jersey. (2024b). *Public Health has published the second part of a report on cancer incidence and mortality rates.*https://www.gov.je/News/2024/pages/publichealthhaspublishedthesecondpartofareportoncancerincidenceandmortalityrates.aspx

Granata, S., Tessari, G., Stallone, G., & Zaza, G. (2023). Skin cancer in solid organ transplant recipients: Still an open problem. *Frontiers in Medicine, 10*, 1189680. https://doi.org/10.3389/fmed.2023.1189680

Hackenbroich, S., Kranke, P., Meybohm, P., & Weibel, S. (2022). Include or not to include conference abstracts in systematic reviews? Lessons learned from a large Cochrane network meta-analysis including 585 trials. *Systematic Reviews, 11*(1), Article 178. https://doi.org/10.1186/s13643-022-02048-6

Han, H. S., & Lubetzky, M. L. (2023). Immune monitoring of allograft status in kidney transplant recipients. *Frontiers in Nephrology, 3*, Article 1293907. https://doi.org/10.3389/fneph.2023.1293907

Harvey, L. A., & Dijkers, M. P. (2019). Should trials that are highly vulnerable to bias be excluded from systematic reviews? *Spinal Cord, 57*(9), 715–716. https://doi.org/10.1038/s41393-019-0340-y

Hay, R. J., Augustin, M., Griffiths, C. E. M., Sterry, W., & Board of the International League of Dermatological Societies and the Grand Challenges Consultation Groups. (2015). The global challenge for skin health. *British Journal of Dermatology, 172*(6), 1469–1472. https://doi.org/10.1111/bjd.13854

Hayashida, M. Z., Fernandes, V. M. C., de Melo Fernandes, D. R., Ogawa, M. M., & Tomimori, J. (2015). Epidemiology and clinical evolution of non-melanoma skin cancer in renal transplant recipients: A single-center experience in São Paulo, Brazil. *International Journal of Dermatology, 54*(10), e383–e388. https://doi.org/10.1111/ijd.12632

Heale, R., & Twycross, A. (2015). Validity and reliability in quantitative studies. *Evidence-Based Nursing, 18*(3), 66–67.

Hennawy, H. M. E., Safar, O., Nassar, A., El Madawie, M. Z., Zaitoun, M. F., Almahdi, Y. M., Al Faifi, A. S., & Tawhari, I. (2025). Belatacept and non-melanoma skin cancer risk in kidney transplant recipients: A narrative review from a mechanistic and clinical perspective. *BMC Nephrology, 26*, Article 487. https://doi.org/10.1186/s12882-025-04373-z

Higgins, J. P. T., & Green, S. (Eds.). (n.d.). *Cochrane handbook for systematic reviews of interventions* (Version 6.3). Cochrane. Retrieved February 26, 2025, from https://training.cochrane.org/handbook/current/chapter-03

Higgins, J. P. T., López-López, J. A., Becker, B. J., Davies, S. R., Dawson, S., Grimshaw, J. M., McGuinness, L. A., Moore, T. H. M., Rehfuess, E. A., Thomas, J., & Caldwell, D. M. (2019). Synthesising quantitative evidence in systematic reviews of complex health interventions. *BMJ Global Health, 4*(Suppl 1), e000858. https://doi.org/10.1136/bmjgh-2018-000858

Higgins, J. P. T., Thomas, J., Chandler, J., Cumpston, M., Li, T., Page, M. J., & Welch, V. A. (Eds.). (2024). *Cochrane handbook for systematic reviews of interventions* (Version 6.5). Cochrane. https://www.cochrane.org/authors/handbooks-and-manuals/handbook/current/chapter-14#section-14-2

Hofstra University. (n.d.). *Evidence and study design.* Hofstra University Library Guides. https://libguides.hofstra.edu/SystematicReviews/EvidenceAndStudyDesign

Hussain, Y., & Khan, H. (2022). Immunosuppressive drugs. In *Encyclopedia of Infection and Immunity* (pp. 726–740). Elsevier. https://doi.org/10.1016/B978-0-12-818731-9.00068-9

Institute for Quality and Efficiency in Health Care. (2023). *In brief: How does the immune system work?* In *InformedHealth.org.* National Library of Medicine (US). https://www.ncbi.nlm.nih.gov/books/NBK279364/

International Agency for Research on Cancer. (2024a). *Melanoma of skin fact sheet (GLOBOCAN 2022, Version 1.1).*https://gco.iarc.who.int/media/globocan/factsheets/cancers/16-melanoma-of-skin-fact-sheet.pdf

International Agency for Research on Cancer. (2024b). *Non-melanoma skin cancer fact sheet (GLOBOCAN 2022, Version 1.1).* https://gco.iarc.who.int/media/globocan/factsheets/cancers/17-non-melanoma-skin-cancer-fact-sheet.pdf

International Agency for Research on Cancer. (2025). *Cancer tomorrow: Data visualisation tool.* Global Cancer Observatory. Retrieved April 28, 2025, from https://gco.iarc.who.int/tomorrow/en/dataviz/bubbles?cancers=17_16&years=2025&populations=991_992_993_994_995_996&types=0&mode=cancer&group_populations=1&multiple_cancers=1

International Transplant Skin Cancer Collaborative. (2025a). *About skin cancer.* Retrieved March 18, 2025, from https://www.itscc.org/patients/about-skin-cancer

International Transplant Skin Cancer Collaborative. (2025b). *Home.* Retrieved March 18, 2025, from https://www.itscc.org/

Jahan, N., Naveed, S., Zeshan, M., & Tahir, M. A. (2016). How to conduct a systematic review: A narrative literature review. *Cureus, 8*(11), e864. https://doi.org/10.7759/cureus.864

Jones-Hughes, T., Snowsill, T., Haasova, M., Cooper, C., Rice, S., Glogowska, M., & Woolacott, N. (2016, August). *Immunosuppressive therapy for kidney transplantation in adults: A systematic review and economic model (Health Technology Assessment No. 20.62).* NIHR Journals Library. https://www.ncbi.nlm.nih.gov/books/NBK379773/

Kajiwara, M., & Masuda, S. (2016). Role of mTOR inhibitors in kidney disease. *International Journal of Molecular Sciences, 17*(6), Article 975. https://doi.org/10.3390/ijms17060975

Karlsson, O., Hagberg, O., Nielsen, K., Paoli, J., & Ingvar, Å. (2021). Difference in sun exposure habits between individuals with high and low risk of skin cancer. *Dermatology Practical & Conceptual, 11*(4), e2021090. https://doi.org/10.5826/dpc.1104a90

Kaufmann, R. A., Oberholzer, P. A., Cazzaniga, S., & Hunger, R. E. (2016). Epithelial skin cancers after kidney transplantation: A retrospective single-centre study of 376 recipients. *European Journal of Dermatology, 26*(3), 265–270.

Khanday, S. A., & Khanam, D. (2023). *The research design.* ResearchGate. https://www.researchgate.net/publication/368257495_THE_RESEARCH_DESIGN

Kidney Research UK. (2019). *Research strategy document.* Retrieved March 28, 2025, from https://www.kidneyresearchuk.org/wp-content/uploads/2019/02/Research-Strategy-Document.pdf

Kim, Y. R., Chung, S. W., Kim, M. J., Choi, W. M., Choi, J., Lee, D., Lee, H. C., & Shim, J. H. (2024). Limited generalizability of retrospective single-center cohort study in comparison to multicenter cohort study on prognosis of hepatocellular carcinoma. *Journal of Hepatocellular Carcinoma, 11*, 1235–1249. https://doi.org/10.2147/JHC.S456093

Kohnehshahri, M. K., Sarkesh, A., Khosroshahi, L. M., HajiEsmailPoor, Z., Maleki, A. A., Yousefi, M., & Maleki, L. A. (2023). Current status of skin cancers with a focus on immunology and immunotherapy. *Cancer Cell International, 23*, Article 174. https://doi.org/10.1186/s12935-023-03012-7

Kolaski, K., Logan, L. R., & Ioannidis, J. P. A. (2023). Guidance to best tools and practices for systematic reviews. *Systematic Reviews, 12*(1), Article 96. https://doi.org/10.1186/s13643-023-02255-9

Krásová, M., Sečníková, Z., Göpfertová, D., Hercogová, J., Viklický, O., Jůzlová, K., & Šmerhovský, Z. (2016). Immunosuppressive therapy in the posttransplant period and skin cancer. *Dermatologic Therapy, 29*(6), 433–436. https://doi.org/10.1111/dth.12379

Kreher, M. A., Noland, M. M. B., Konda, S., Longo, M. I., & Valdes-Rodriguez, R. (2023). Risk of melanoma and nonmelanoma skin cancer with immunosuppressants, part I: Calcineurin inhibitors, thiopurines, IMDH inhibitors, mTOR inhibitors, and corticosteroids. *Journal of the American Academy of Dermatology, 88*(3), 521–530. https://doi.org/10.1016/j.jaad.2022.11.044

Krenzien, F., ElKhal, A., Quante, M., Biefer, H. R. C., Hirofumi, U., Gabardi, S., & Tullius, S. G. (2015). A rationale for age-adapted immunosuppression in organ transplantation. *Transplantation, 99*(11), 2258–2268. https://doi.org/10.1097/TP.0000000000000842

Kreuz, M., Cardoso, J. C. O., Sobreira, L. E. R., Cavalcanti Souza, M. E., Campos, L. E., Kelly, F. A., & de Moraes, F. C. A. (2025). Azathioprine and risk of non-melanoma skin cancers in organ transplant recipients: A systematic review and update meta-analysis. *Clinical and Translational Oncology*, 1–10. https://doi.org/10.1007/s12094-024-03839-0

Lame, G. (2019). Systematic literature reviews: An introduction. In *Proceedings of the 22nd International Conference on Engineering Design (ICED19)* (pp. 1639–1648). https://doi.org/10.1017/dsi.2019.169

Lasserson, T. J., Thomas, J., & Higgins, J. P. T. (2024). Chapter 1: Starting a review. In J. P. T. Higgins, J. Thomas, J. Chandler, M. Cumpston, T. Li, M. J. Page, & V. A. Welch (Eds.), *Cochrane handbook for systematic reviews of interventions* (Version 6.5). Cochrane. https://training.cochrane.org/handbook/current/chapter-01

Lee, S. W., and Koo, M. J. (2022). PRISMA 2020 statement and guidelines for systematic review and meta-analysis articles, and their underlying mathematics: Life Cycle Committee recommendations. *Life Cycle, 2*, Article eLC-2-0-9. https://doi.org/10.54724/lc.2022.eLC-2-0-9

Lefebvre, C., Glanville, J., Briscoe, S., Featherstone, R., Littlewood, A., Metzendorf, M.-I., Noel-Storr, A., Paynter, R., Rader, T., Thomas, J., & Wieland, L. S. (2025). Searching for and selecting studies. In J. P. T. Higgins, J. Thomas, J. Chandler, M. Cumpston, T. Li, M. J. Page, & V. A. Welch (Eds.), *Cochrane handbook for systematic reviews of interventions* (Version 6.5.1, Chapter 4). Cochrane. https://training.cochrane.org/handbook

Leonhard, J., Schaier, M., Kälble, F., Zeier, M., & Steinborn, A. (2023). Exhaustion of $CD8^+$ central memory responder T cell differentiation provokes non-melanoma skin cancer in elderly kidney transplant recipients. *Frontiers in Immunology, 14*, Article 1164284. https://doi.org/10.3389/fimmu.2023.1164284

Lim, W. H., Russ, G. R., Wong, G., Pilmore, H., Kanellis, J., & Chadban, S. J. (2017). The risk of cancer in kidney transplant recipients may be reduced in those maintained on everolimus and reduced cyclosporine. *Kidney International, 91*(4), 954–963. https://doi.org/10.1016/j.kint.2016.11.008

Long, H. A., French, D. P., & Brooks, J. M. (2020). Optimising the value of the Critical Appraisal Skills Programme (CASP) tool for quality appraisal in qualitative evidence synthesis. *Research Methods in Medicine and Health Sciences, 1*(1), 31–42. https://doi.org/10.1177/2632084320947559

Ma, J. E., & Brewer, J. D. (2014). Merkel cell carcinoma in immunosuppressed patients. *Cancers, 6*(3), 1328–1350. https://doi.org/10.3390/cancers6031328

Ma, L. L., Wang, Y. Y., Yang, Z. H., Huang, D., Weng, H., Zeng, X. T., & Chen, H. (2020). Methodological quality (risk of bias) assessment tools for primary and secondary medical studies: What are they and which is better? *Military Medical Research, 7*(1), Article 7. https://doi.org/10.1186/s40779-020-00238-8

Ma, M. K. M., Lim, W. H., Turner, R. M., Chapman, J. R., Craig, J. C., & Wong, G. (2014). The risk of cancer in recipients of living-donor, standard and expanded criteria deceased donor kidney transplants: A registry analysis. *Transplantation, 98*(12), 1286–1293. https://doi.org/10.1097/TP.0000000000000375

Maddox, J. S., & Soltani, K. (2008). Risk of nonmelanoma skin cancer with azathioprine use. *Inflammatory Bowel Diseases, 14*(10), 1425–1431. https://doi.org/10.1002/ibd.20444

Malagón-Liceaga, A., Bermúdez-Rodríguez, S. P., Romero-Aguila, J. A., Carolina, L. J. F., Palafox-Romo, R., Díaz-Sánchez, V. M., Marino-Vazquez, L., Morales-Beunrostro, L. E., Gomez, J. A., Dominguez-Cherit, J., & Ruelas-Villavicencio, A. L. (2024). Skin cancer incidence in Mexican renal

transplant recipients: A cohort over 56 years. *International Journal of Dermatology, 63*(11), e315–e321. https://doi.org/10.1111/ijd.17332

Massicotte-Azarniouch, D., Noel, J. A., & Knoll, G. A. (2024). Epidemiology of cancer in kidney transplant recipients. *Seminars in Nephrology, 44*(3), Article 151494. https://doi.org/10.1016/j.semnephrol.2024.151494

McKeaveney, C., Noble, H., Courtney, A. E., Gill, P., Griffin, S., Johnston, W., Maxwell, A. P., Teasdale, F., & Reid, J. (2020). Understanding the holistic experiences of living with a kidney transplant: An interpretative phenomenological study (protocol). *BMC Nephrology, 21*(1), Article 222. https://doi.org/10.1186/s12882-020-01860-3

McKenzie, J. E., & Brennan, S. E. (2019). Synthesizing and presenting findings using other methods. In J. P. T. Higgins, J. Thomas, J. Chandler, M. Cumpston, T. Li, M. J. Page, & V. A. Welch (Eds.), *Cochrane handbook for systematic reviews of interventions* (Version 6.5). Cochrane. Retrieved June 14, 2025, from https://www.cochrane.org/handbook

Meneghini, M., Bestard, O., & Grinyó, J. M. (2021). Immunosuppressive drugs modes of action. *Best Practice & Research Clinical Gastroenterology, 54*, Article 101757. https://doi.org/10.1016/j.bpg.2021.101757

Mittal, A., & Colegio, O. R. (2017). Skin cancers in organ transplant recipients. *American Journal of Transplantation, 17*(10), 2509–2530. https://doi.org/10.1111/ajt.14382

Murray, S. L., Daly, F. E., O'Kelly, P., O'Leary, E., Deady, S., O'Neill, J. P., Dudley, A., Rutledge, N. R., McCormick, A., Houlihan, D. D., Williams, Y., Morris, P. G., Ní Raghallaigh, S., Moloney, F. J., Sexton, D. J., & Conlon, P. J. (2020). The impact of switching to mTOR inhibitor-based immunosuppression on long-term non-melanoma skin cancer incidence and renal function in kidney and liver transplant recipients. *Renal Failure, 42*(1), 607–612. https://doi.org/10.1080/0886022X.2020.1785499

Musalem, P., & Sáez-Vera, C. (2025). Forty years of kidney transplantation: Insights into malignancies at a single center in Latin America. *Transplant Immunology, 90*, Article 102216. https://doi.org/10.1016/j.trim.2025.102216

Nadelson, S., & Nadelson, L. S. (2014). Evidence-based practice article reviews using CASP tools: A method for teaching EBP. *Worldviews on Evidence-Based Nursing, 11*(5), 344–346. https://doi.org/10.1111/wvn.12059

Naik, R. H., & Shawar, S. H. (2023). *Renal transplantation rejection*. StatPearls Publishing. https://www.ncbi.nlm.nih.gov/books/NBK553074/

National Institute for Health and Care Excellence. (2017). *Immunosuppressive therapy for kidney transplant in adults (Technology appraisal guidance TA481)*. https://www.nice.org.uk/guidance/ta481/resources/immunosuppressive-therapy-for-kidney-transplant-in-adults-pdf-82605021450181

National Institute for Health and Care Excellence. (2022). *Introduction to real world evidence in NICE decision-making*. In *NICE real world evidence framework* (ECD9). https://www.nice.org.uk/corporate/ecd9/chapter/introduction-to-real-world-evidence-in-nice-decision-making

National Kidney Foundation. (2023). *Kidney failure*. Retrieved March 20, 2025, from https://www.kidney.org/kidney-topics/kidney-failure

National Kidney Foundation. (2024). *Immunosuppressants (anti-rejection medicines)*. Retrieved March 18, 2025, from https://www.kidney.org/kidney-topics/immunosuppressants-anti-rejection-medicines

National Kidney Registry. (2025). *Finding the best kidney transplant match*. Retrieved March 20, 2025, from https://www.kidneyregistry.com/for-patients/finding-the-best-kidney-match/

Okut, G., Alp, A., Tatar, E., Simsek, C., Tugmen, C., & Uslu, A. (2017). Nonmelanoma skin cancers after kidney transplant: Our 15 years of experience with mammalian target of rapamycin inhibitors. *Experimental*

and Clinical Transplantation, 15(Suppl 1), 236–239. https://doi.org/10.6002/ect.mesot2016.P112

Olaghere, A., Wilson, D. B., & Kimbrell, C. (2023). Inclusive critical appraisal of qualitative and quantitative findings in evidence synthesis. *Research Synthesis Methods, 14*(6), 847–852. https://doi.org/10.1002/jrsm.1659

Opelz, G., Unterrainer, C., Süsal, C., & Döhler, B. (2016). Immunosuppression with mammalian target of rapamycin inhibitor and incidence of post-transplant cancer in kidney transplant recipients. *Nephrology Dialysis Transplantation, 31*(8), 1360–1367. https://doi.org/10.1093/ndt/gfw088

Oweira, H., Ramouz, A., Ghamarnejad, O., Khajeh, E., Ali-Hasan-Al-Saegh, S., Nikbakhsh, R., Reißfelder, C., Rahbari, N., Mehrabi, A., & Sadeghi, M. (2022). Risk factors of rejection in renal transplant recipients: A narrative review. *Journal of Clinical Medicine, 11*(5), Article 1392. https://doi.org/10.3390/jcm11051392

Owens, J. K. (2021). Systematic reviews: Brief overview of methods, limitations, and resources. *Nurse Author & Editor, 31*(3–4), 69–72. https://doi.org/10.1111/nae2.28

Pacheco, R. L., Riera, R., Santos, G. M., Sá, K. M. M., Bomfim, L. G. P., da Silva, G. R., de Oliveira, F. R., & Martimbianco, A. L. C. (2023). Many systematic reviews with a single author are indexed in PubMed. *Journal of Clinical Epidemiology, 156*, 124–126.

Page, M. J., McKenzie, J. E., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., Shamseer, L., Tetzlaff, J. M., Akl, E. A., Brennan, S. E., Chou, R., Glanville, J., Grimshaw, J. M., Hróbjartsson, A., Lalu, M. M., Li, T., Loder, E. W., Mayo-Wilson, E., McDonald, S., … & Moher, D. (2021). The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *BMJ, 372*, n71. https://doi.org/10.1136/bmj.n71

Pannucci, C. J., & Wilkins, E. G. (2010). Identifying and avoiding bias in research. *Plastic and Reconstructive Surgery, 126*(2), 619–625. https://doi.org/10.1097/PRS.0b013e3181de24bc

Park, Y. S., Konge, L., & Artino, A. R., Jr. (2020). The positivism paradigm of research. *Academic Medicine, 95*(5), 690–694. https://doi.org/10.1097/ACM.0000000000003093

Parker, E. R. (2020). The influence of climate change on skin cancer incidence: A review of the evidence. *International Journal of Women's Dermatology, 7*(1), 17–27. https://doi.org/10.1016/j.ijwd.2020.07.003

Patel, P. (2009). Introduction to quantitative methods. *Empirical Law Seminar, 14*(1), 1–14.

Pearson, A., White, H., Bath-Hextall, F., Salmond, S., Apostolo, J., & Kirkpatrick, P. (2015). A mixed-methods approach to systematic reviews. *JBI Evidence Implementation, 13*(3), 121–131. https://doi.org/10.1097/XEB.0000000000000052

Pickering, C., Grignon, J., Steven, R., Guitart, D., & Byrne, J. (2015). Publishing not perishing: How research students transition from novice to knowledgeable using systematic quantitative literature reviews. *Studies in Higher Education, 40*(10), 1756–1769. https://doi.org/10.1080/03075079.2014.914907

Pinho, A., Gouveia, M., Cardoso, J. C., Xavier, M. M., Vieira, R., & Alves, R. (2016). Non-melanoma skin cancer in Portuguese kidney transplant recipients: Incidence and risk factors. *Anais Brasileiros de Dermatologia, 91*(4), 455–462. https://doi.org/10.1590/abd1806-4841.20164891

Pisano, C., Leitenberger, J. J., Pugliano-Mauro, M., & Carroll, B. T. (2024). Updates in skin cancer in transplant recipients and immunosuppressed patients: Review of the 2022–2023 scientific symposium of the International Immunosuppression and Transplant Skin Cancer Collaborative. *Transplant International, 37*, Article 12387. https://doi.org/10.3389/ti.2024.12387

Pluye, P., Gagnon, M. P., Griffiths, F., & Johnson-Lafleur, J. (2009). A scoring system for appraising mixed methods research, and concomitantly appraising qualitative, quantitative and mixed methods primary studies in mixed studies reviews. *International Journal of Nursing Studies, 46*(4), 529–546. https://doi.org/10.1016/j.ijnurstu.2009.01.009

Purssell, E. (2020). Can the Critical Appraisal Skills Programme checklists (CASP) be used alongside GRADE (Grading of Recommendations Assessment, Development and Evaluation) to improve transparency and decision-making? *Journal of Advanced Nursing, 76*(4), 1082–1089. https://doi.org/10.1111/jan.14303

Rai, H. K., Cavalcanti Barroso, A., Yates, L., Schneider, J., & Orrell, M. (2020). Involvement of people with dementia in the development of technology-based interventions: Narrative synthesis review and best practice guidelines. *Journal of Medical Internet Research, 22*(12), e17531. https://doi.org/10.2196/17531

Randles, R., & Finnegan, A. (2023). Guidelines for writing a systematic review. *Nurse Education Today, 125*, Article 105803.

Reeves, B. C., Deeks, J. J., Higgins, J. P. T., Shea, B., Tugwell, P., & Wells, G. A. (2019). Chapter 24: Including non-randomized studies on intervention effects. In J. P. T. Higgins, J. Thomas, J. Chandler, M. Cumpston, T. Li, M. J. Page, & V. A. Welch (Eds.), *Cochrane handbook for systematic reviews of interventions* (Version 6.5). Cochrane. Retrieved July 17, 2025, from https://www.cochrane.org/authors/handbooks-and-manuals/handbook/current/chapter-24

Roky, A. H., Islam, M. M., Ahasan, A. M. F., Mostaq, M. S., Mahmud, M. Z., Amin, M. N., & Mahmud, M. A. (2025). Overview of skin cancer types and prevalence rates across continents. *Cancer Pathogenesis and Therapy, 3*(2), 89–100. https://doi.org/10.1016/j.cpt.2024.08.002

Rollan, M. P., Cabrera, R., & Schwartz, R. A. (2022). Current knowledge of immunosuppression as a risk factor for skin cancer development. *Critical Reviews in Oncology/Hematology, 177*, Article 103754. https://doi.org/10.1016/j.critrevonc.2022.103754

Ruggenenti, P., Cravedi, P., Gotti, E., Plati, A., Marasà, M., Sandrini, S., … Remuzzi, G. (2021). Mycophenolate mofetil versus azathioprine in kidney transplant recipients on steroid-free, low-dose cyclosporine immunosuppression (ATHENA): A pragmatic randomized trial. *PLoS Medicine, 18*(6), e1003668. https://doi.org/10.1371/journal.pmed.1003668

Ryan, R. (2013). *Cochrane Consumers and Communication Review Group: Data synthesis and analysis*. Cochrane Consumers and Communication Review Group. http://cccrg.cochrane.org

Sachedina, D., Gibson, F., Xia, E., Walia, A., Behara, L., Fazelpour, S., Mullins, H., Francis, J., & Sahni, D. (2024). Skin cancer in renal transplant recipients: Outcomes from a safety net hospital in Boston. *International Journal of Dermatology, 63*(8), 1048–1055. https://doi.org/10.1111/ijd.17061

Sarri, G., Patorno, E., Yuan, H., Guo, J. J., Bennett, D., Wen, X., Zullo, A. R., Largent, J., Panaccio, M., Gokhale, M., Moga, D. C., Ali, M. S., & Debray, T. P. (2022). Framework for the synthesis of non-randomised studies and randomised controlled trials: A guidance on conducting a systematic review and meta-analysis for healthcare decision making. *BMJ Evidence-Based Medicine, 27*(2), 109–119. https://doi.org/10.1136/bmjebm-2020-111493

Scherer, R. W., & Saldanha, I. J. (2019). How should systematic reviewers handle conference abstracts? A view from the trenches. *Systematic Reviews, 8*(1), Article 264. https://doi.org/10.1186/s13643-019-1188-0

Schünemann, H. J., Higgins, J. P. T., Vist, G. E., Glasziou, P., Akl, E. A., Skoetz, N., & Guyatt, G. H. (2024a). Chapter 14: Completing “Summary of findings” tables and grading the certainty of the evidence. In J. P. T. Higgins, J.

Thomas, J. Chandler, M. Cumpston, T. Li, M. J. Page, & V. A. Welch (Eds.), *Cochrane handbook for systematic reviews of interventions* (Version 6.5). Cochrane. https://www.cochrane.org/authors/handbooks-and-manuals/handbook/current/chapter-14

Schünemann, H. J., Vist, G. E., Higgins, J. P. T., Santesso, N., Deeks, J. J., Glasziou, P., Akl, E. A., & Guyatt, G. H. (2024b). Chapter 15: Interpreting results and drawing conclusions. In J. P. T. Higgins, J. Thomas, J. Chandler, M. Cumpston, T. Li, M. J. Page, & V. A. Welch (Eds.), *Cochrane handbook for systematic reviews of interventions* (Version 6.5). Cochrane. https://www.cochrane.org/handbook

Schünemann, H., Brożek, J., Guyatt, G., & Oxman, A. (Eds.). (2013). *GRADE handbook for grading quality of evidence and strength of recommendations*. The GRADE Working Group. https://gdt.gradepro.org/app/handbook/handbook.html

Scott, S., Shireen, G. R., Rachel, F., Kirsner, R. S., & Maderal, A. D. (2022). Malignancy risk of non-biologic immunosuppressive therapies: A review of the literature with evidence-based treatment recommendations. *Experimental Dermatology, 31*(11), 1656–1664. https://doi.org/10.1111/exd.14647

Seth, D., Cheldize, K., Brown, D., & Freeman, E. F. (2017). Global burden of skin disease: Inequities and innovations. *Current Dermatology Reports, 6*(3), 204–210. https://doi.org/10.1007/s13671-017-0192-7

Setia, M. S. (2016). Methodology series module 1: Cohort studies. *Indian Journal of Dermatology, 61*(1), 21–25. https://doi.org/10.4103/0019-5154.174011

Shao, E. X., Betz-Stablein, B., Marquat, L., Campbell, S., Isbel, N., Green, A. C., & Plasmeijer, E. I. (2022). Higher mycophenolate dosage is associated with an increased risk of squamous cell carcinoma in kidney transplant recipients. *Transplant Immunology, 75*, Article 101698. https://doi.org/10.1016/j.trim.2022.101698

Shope, C. N., Andrews, L. A., Neimy, H., Linkous, C. L., Khamdan, F., & Lee, L. W. (2023). Characterizing skin cancer in transplant recipients by Fitzpatrick skin phototype. *Dermatology and Therapy, 13*(1), 147–154. https://doi.org/10.1007/s13555-022-00858-z

Shreffler, J., & Huecker, M. R. (2023). Hypothesis testing, p values, confidence intervals, and significance. In *StatPearls*. StatPearls Publishing. Retrieved January 2025, from https://www.ncbi.nlm.nih.gov/books/NBK557421/

Shrier, I., Boivin, J. F., Platt, R. W., Steele, R. J., Brophy, J. M., Carnevale, F., Ducharme, F., & Rossignol, M. (2008). The interpretation of systematic reviews with meta-analyses: An objective or subjective process? *BMC Medical Informatics and Decision Making, 8*(1), Article 19. https://doi.org/10.1186/1472-6947-8-19

Siddaway, A. P., Wood, A. M., & Hedges, L. V. (2019). How to do a systematic review: A best practice guide for conducting and reporting narrative reviews, meta-analyses, and meta-syntheses. *Annual Review of Psychology, 70*(1), 747–770. https://doi.org/10.1146/annurev-psych-010418-102803

Sileyew, K. J. (2020). *Research design and methodology*. IntechOpen. https://doi.org/10.5772/intechopen.85731

Singh, J. (2013). Critical appraisal skills programme. *Journal of Pharmacology and Pharmacotherapeutics, 4*(1), 76–77. https://doi.org/10.4103/0976-500X.107697

Smith, A., Niu, W., & Desai, A. (2017). The effect of conversion from a calcineurin inhibitor to sirolimus on skin cancer reduction in post-renal transplantation patients. *Cureus, 9*(8), Article e1564. https://doi.org/10.7759/cureus.1564

Smith, J., & Noble, H. (2025). Understanding sources of bias in research. *Evidence-Based Nursing, 28*(3), 137–139.

Snyder, H. (2019). Literature review as a research methodology: An overview and guidelines. *Journal of Business Research, 104*, 333–339. https://doi.org/10.1016/j.jbusres.2019.07.039

Song, F., Hooper, L., & Loke, Y. K. (2013). Publication bias: What is it? How do we measure it? How do we avoid it? *Open Access Journal of Clinical Trials*, 71–81. https://doi.org/10.2147/OAJCT.S34419

Stasko, T., & Hanlon, A. M. (2023). Prevention and management of skin cancer in solid organ transplant recipients. *UpToDate*. Retrieved March 1, 2025, from https://www.uptodate.com/contents/prevention-and-management-of-skin-cancer-in-solid-organ-transplant-recipients

Steer, P. J., & Ernst, S. (2021). Peer review—Why, when and how. *International Journal of Cardiology Congenital Heart Disease, 2*, Article 100083. https://doi.org/10.1016/j.ijcchd.2021.100083

Sterne, J. A. C., Hernán, M. A., Reeves, B. C., Savović, J., Berkman, N. D., Viswanathan, M., Henry, D., Altman, D. G., Ansari, M. T., Boutron, I., Carpenter, J. R., Chan, A. W., Churchill, R., Deeks, J. J., Hrobjartsson, A., Kirkham, J., Juni, P., Loke, Y. K., Pigott. T. D., … Higgins, J. P. T. (2016). ROBINS-I: A tool for assessing risk of bias in non-randomised studies of interventions. *BMJ, 355*, i4919. https://doi.org/10.1136/bmj.i4919

Sterne, J. A. C., Savović, J., Page, M. J., Elbers, R. G., Blencowe, N. S., Boutron, I., Cates, C. J., Cheng, H.-Y., Corbett, M. S., Eldridge, S. M., Emberson, J. R., Hernán, M. A., Hopewell, S., Hróbjartsson, A., Junqueira, D. R., Jüni, P., Kirkham, J. J., Lasserson, T., Li, T., **...** Higgins, J. P. T. (2019). RoB 2: A revised tool for assessing risk of bias in randomised trials. *BMJ, 366*, l4898. https://doi.org/10.1136/bmj.l4898

Stoll, C. R. T., Izadi, S., Fowler, S., Green, P., Suls, J., & Colditz, G. A. (2019). The value of a second reviewer for study selection in systematic reviews. *Research Synthesis Methods, 10*(4), 539–545. https://doi.org/10.1002/jrsm.1369

Struckmeier, A. K., Gosau, M., & Smeets, R. (2024). Cutaneous squamous cell carcinoma in solid organ transplant recipients: Current therapeutic and screening strategies. *Transplantation Reviews, 38*(4), Article 100882. https://doi.org/10.1016/j.trre.2024.100882

Sułowicz, J., Wojas-Pelc, A., Ignacak, E., Krzanowska, K., Kuźniewski, M., & Sułowicz, W. (2017). Comparison of the incidence of skin cancers in patients on dialysis and after kidney transplantation. *Advances in Dermatology and Allergology, 34*(2), 138–142. https://doi.org/10.5114/ada.2017.67078

Suri, H. (2020). Ethical considerations of conducting systematic reviews in educational research. In *Systematic reviews in educational research: Methodology, perspectives and application* (pp. 41–54). https://doi.org/10.1007/978-3-658-27602-7_3

Szumilas, K., Wilk, A., Wiśniewski, P., Gimpel, A., Dziedziejko, V., Kipp, M., & Pawlik, A. (2023). Current status regarding immunosuppressive treatment in patients after renal transplantation. *International Journal of Molecular Sciences, 24*(12), Article 10301. https://doi.org/10.3390/ijms241210301

Tantisattamo, E., Maggiore, U., & Piccoli, G. B. (2022). History of kidney transplantation: A journey of progression and evolution for success. *Journal of Nephrology, 35*, 1783–1786. https://doi.org/10.1007/s40620-022-01453-3

Thet, Z., Lam, A. K. Y., Ng, S. K., Aung, S. Y., Han, T., Ranganathan, D., Gobe, G. C., & Khoo, T. K. (2024). Comparison of skin cancer risk between renal transplant recipients and patients with glomerular diseases in rural Queensland. *Australian Journal of Rural Health, 32*(2), 249–262. https://doi.org/10.1111/ajr.13081

Thomson, H., Campbell, M., Katikireddi, S. V., & Sowden, A. (2018, September 16). Improving the reporting and conduct of narrative synthesis of quantitative data (ICONS Quant): A pilot of the ICONS Quant tool

[Workshop session]. 25th Cochrane Colloquium, Edinburgh, United Kingdom. Retrieved from https://colloquium2018.cochrane.org/workshops/improving-reporting-and-conduct-narrative-synthesis-quantitative-data-icons-quant-pilot

Tofthagen, C. (2012). Threats to validity in retrospective studies. *Journal of the Advanced Practitioner in Oncology, 3*(3), 181.

Turnbull, D., Chugh, R., & Luck, J. (2023). Systematic-narrative hybrid literature review: A strategy for integrating a concise methodology into a manuscript. *Social Sciences & Humanities Open, 7*(1), Article 100381. https://doi.org/10.1016/j.ssaho.2022.100381

Uttley, L., Quintana, D. S., Montgomery, P., Carroll, C., Page, M. J., Falzon, L., Haber, N., & Moher, D. (2023). The problems with systematic reviews: A living systematic review. *Journal of Clinical Epidemiology, 156*, 30–41. https://doi.org/10.1016/j.jclinepi.2023.01.011

Varkey, B. (2021). Principles of clinical ethics and their application to practice. *Medical Principles and Practice: International Journal of the Kuwait University, Health Science Centre, 30*(1), 17–28. https://doi.org/10.1159/000509119

Wadhawan, M., & Gupta, C. (2023). Immunosuppression monitoring—What clinician needs to know? *Journal of Clinical and Experimental Hepatology, 13*(4), 691–697. https://doi.org/10.1016/j.jceh.2023.01.003

Wallace, S. S., Barak, G., Truong, G., & Parker, M. W. (2022). Hierarchy of evidence within the medical literature. *Hospital Pediatrics, 12*(8), 745–750. https://doi.org/10.1542/hpeds.2022-006690

Walpole, S. C. (2019). Including papers in languages other than English in systematic reviews: Important, feasible, yet often omitted. *Journal of Clinical Epidemiology, 111*, 127–134. https://doi.org/10.1016/j.jclinepi.2019.03.004

Wang, X., & Kattan, M. W. (2020). Cohort studies: Design, analysis, and reporting. *Chest, 158*(1), S72–S78. https://doi.org/10.1016/j.chest.2020.03.014

Waring Historical Library. (n.d.). *A timeline of kidney transplantation*. Medical University of South Carolina. Retrieved March 30, 2025, from https://waring.library.musc.edu/exhibits/kidney/Transplantation.php

Wheless, L., Anand, N., Hanlon, A., & Chren, M. M. (2022). Differences in skin cancer rates by transplanted organ type and patient age after organ transplant in White patients. *JAMA Dermatology, 158*(11), 1287–1292. https://doi.org/10.1001/jamadermatol.2022.3878

Wiseman, A. C. (2016). Immunosuppressive medications. *Clinical Journal of the American Society of Nephrology, 11*(2), 332–343. https://doi.org/10.2215/CJN.08570814

Wojciechowski, D., & Wiseman, A. (2021). Long-term immunosuppression management: Opportunities and uncertainties. *Clinical Journal of the American Society of Nephrology, 16*(8), 1264–1271. https://doi.org/10.2215/CJN.08570814

World Cancer Research Fund. (2024). Skin cancer statistics. Retrieved March 18, 2025, from https://www.wcrf.org/preventing-cancer/cancer-statistics/skin-cancer-statistics/

Wunderlich, K., Suppa, M., Gandini, S., Lipski, J., White, J. M., & Del Marmol, V. (2024). Risk factors and innovations in risk assessment for melanoma, basal cell carcinoma, and squamous cell carcinoma. *Cancers, 16*(5), 1016. https://doi.org/10.3390/cancers16051016

Yatim, K. M., & Lakkis, F. G. (2015). A brief journey through the immune system. *Clinical Journal of the American Society of Nephrology, 10*(7), 1274–1281. https://doi.org/10.2215/CJN.10031014

Ying, T., Wong, G., Lim, W., Kanellis, J., Pilmore, H., Campbell, S., McDonald, S., & Chadban, S. (2018). De novo or early conversion to everolimus and long-term cancer outcomes in kidney transplant recipients: A trial-based linkage study. *American Journal of Transplantation, 18*(12), 2977–2986. https://doi.org/10.1111/ajt.14948

Zeng, X.-T., Zhang, Y., Kwong, J. S. W., Zhang, C., Li, S., Sun, F., Niu, Y., & Du, L. (2015). The methodological quality assessment tools for preclinical and clinical studies, systematic review and meta-analysis, and clinical practice guideline: A systematic review. *Journal of Evidence-Based Medicine, 8*(1), 2–10. https://doi.org/10.1111/jebm.12141

Appendices

Appendix 1: PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each	

Section and Topic	Item #	Checklist item	Location where item is reported
		outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	

Section and Topic	Item #	Checklist item	Location where item is reported
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	
Study characteristics	17	Cite each included study and present its characteristics.	
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	
	23b	Discuss any limitations of the evidence included in the review.	
	23c	Discuss any limitations of the review processes used.	
	23d	Discuss implications of the results for practice, policy, and future research.	
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	

Section and Topic	Item #	Checklist item	Location where item is reported
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	
Competing interests	26	Declare any competing interests of review authors.	
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	

Appendix 2: Ethical form systematic review

Student Systematic Review Form

Section 1: Applicant Details	
Applicant Name:	Amber Sullivan
Student number:	1724112
Programme of study:	MSc Professional Studies
Correspondence Address:	Jersey General Hospital, The Parade, St. Helier, Jersey, JE1 3QS
Email address:	1724112@chester.ac.uk

	Please Tick ✓
I confirm that this is a student project for a PGT or PGR academic award.	✓

Section 2: Supervisor Details	
Name of Supervisor:	Dr Moyra Journeaux
Email Address:	m.journeaux@health.gov.je

Section 3: Systematic Review Details

Title of systematic review or review of literature (please give full title):

Is there an association between immunosuppression and skin cancer risk in kidney transplant recipients? A Systematic Review of the literature

Question	Yes	No	If Yes please provide further detail
Does the project involve human participants, either directly (e.g. through use of interviews, questionnaires)		✓	
Or indirectly (e.g. through provision of, or access to, a person's data).		✓	

Please complete the following if you have answered **No** to the previous two questions:

Question	Yes	No	If Yes please provide further detail
1. Does the title identify the work as a systematic review or review of the literature, or both?	✓		Identifies that the research will be focused on being a systematic review
2. Is the question posed original and well defined?	✓		PICO used to frame the question P kidney transplant recipients I use of immunosuppression C no comparison used O Increased risk of developing skin cancer
3. Will the work affect the confidentiality originally promised to study participants?		✓	Not applicable – no participants will be included
4. Will you be contacting the original researchers for more information?		✓	It is not planned to do this unless this is considered appropriate when research studies are

			retrieved and reviewed, and further information is required.

Description of Project (250 words)

Patients who have a kidney transplant go on to using immunosuppression medication long-term as a treatment to preserve the transplanted kidney and preventing rejection (National Kidney Foundation, 2024). The long term use of immunosuppression has been recognised for being a potential cause of skin cancers (Massicotte-Azarniouch, Noel, & Knoll, 2024). However, it is difficult to prove a direct causal relationship, due to other associated factors. The aim of this systematic review is to analyse existing literature on the association between post-renal transplant immunosuppression and the increased risk of developing skin cancer. It will aim to analyse the published literature surrounding the use of immunosuppression in post kidney transplant patients and their direct risks for skin cancer. The focus will be on the combination of existing studies, to help understand the relationship between the cause and effect, whilst also identifying any patterns or trends. The strength of the evidence will be assessed to determine the clinical implications for transplant recipients. The information collected will be sourced from multiple databases including, Cochrane, Pubmed, Medline and Proquest. The eligibility of these sources will be guided by Cochrane and PRISMA, as to ensure the correct standards are being followed.

Ethical approval will not be required due to the review not involving any primary research or participant involvement; however, ethical considerations will still be mediated, with ethical principles being considered. Cochrane highlights the essential use for systematic reviews in ensuring that information regarding patients and their care is sought from having an up-to-date and complete overview of all the essential information needed. This ensures the ethical principal '**Beneficence' which emphasises to do good and be of benefit to others.** By undertaking this systematic review, it will potentially help to endorse the current leading research, while providing the need for ongoing exploration within this area.

Section 4: Declarations & Signatures Please Tick ✓	✓
We confirm that we have reviewed the project protocol and checked http://www.hra.nhs.uk/documents/2016/06/defining-research.pdf to define the project category.	✓
If you have answered **No** to question 3 and 4 above you will only need to have the form signed by your supervisor and then you send it to hscethics@chester.ac.uk and your approval letter will be sent to you. If you answer **Yes** to Q3 and 4 above please complete the comment box and submit to hscethics@chester.ac.uk. This form will then be reviewed by the Chair of Ethics before it is approved	✓
We conclude that the project is not research and does not require ethical or scientific merit review.	✓

Signatures	
Applicant: A.Sullivan	Date: 25th February 2025
Supervisor: Moyra Tourneau	Date: 25 February 2025

Appendix 3: CASP Checklist

3.1 Randomised Controlled Trials (RCTs)

Reviewer Name:	Amber Sullivan
Paper Title:	Sirolimus for secondary prevention of skin cancer in kidney transplant recipients: 5-year results.
Author:	Dantal et al. (2018)
Web Link:	https://ascopubs.org/doi/full/10.1200/JCO.2017.76.6691
Appraisal Date:	17th August 2025

Section A Is the basic study design valid for a randomised controlled trial?	
1. Did the study address a clearly formulated research question? • Yes, this was an extension to 5 year follow up of KTRs on a sirolimus regimen vs CNI and the risks associated with SCC and BCC	Yes **X** No Can't Tell
CONSIDER: *Was the study designed to assess the outcomes of an intervention?* *Is the research question 'formulated' in terms of:* • *Population studied* • *Intervention given* • *Comparator chosen* • *Outcomes measured?*	
2. Was the assignment of participants to interventions randomised? • 1-1 ratio for randomisation • Lack of details – noted randomly assigned, but not sure how	Yes No Can't Tell **X**
CONSIDER: • *How was randomisation carried out? Was the method appropriate?* • *Was randomisation sufficient to eliminate systematic bias?* • *Was the allocation sequence concealed from investigators and participants?*	
3. Were all participants who entered the study accounted for at its conclusion? • All losses to follow up noted in tabular format	Yes **X** No Can't Tell
CONSIDER: • *Were losses to follow-up and exclusions after randomisation accounted for?* • *Were participants analysed in the study groups to which they were randomised (intention-to-treat analysis)?* • *Was the study stopped early? If so, what was the reason?*	
Section B Was the study methodologically sound?	
4. (a) Were the participants 'blind' to intervention they were given? • Was open-label. Not blinded	Yes No **X** Can't Tell
(b) Were the investigators 'blind' to the intervention they were giving to participants? • Was open-label. Not blinded	Yes No **X** Can't Tell
(c) Were the people assessing/analysing outcome/s 'blinded'?	Yes No **X**

• Was open-label. Not blinded	Can't Tell
5. Were the study groups similar at the start of the randomised controlled trial? • Baseline characteristics noted • All must have had at least one SCC post-transplant to participate	Yes **X** No Can't Tell
CONSIDER: • *Were the baseline characteristics of each study group (e.g. age, sex, socio-economic group) clearly set out?* • *Were there any differences between the study groups that could affect the outcome/s?*	
6. Apart from the experimental intervention, did each study group receive the same level of care (that is, were they treated equally)? • Clear study protocol described • All follow ups the same – every 3 months for first 2 years and then every 6 months until the 5 years	Yes **X** No Can't Tell
CONSIDER: • *Was there a clearly defined study protocol?* • *If any additional interventions were given (e.g. tests or treatments), were they similar between the study groups?* • *Were the follow-up intervals the same for each study group?*	
Section C: What are the results?	
7. Were the effects of intervention reported comprehensively? • Primary outcome: no new SCC at 5 years post transplants • Secondary outcome: the time of onset for new SCC post-transplant • P values reported • Hazard ratio reported • Adverse effects and dropouts included – similar in both study groups, however risks for attrition bias due to the distribution • Selection bias – randomisation however small sample size for study	Yes **X** No Can't Tell
CONSIDER: • *Was a power calculation undertaken?* • *What outcomes were measured, and were they clearly specified?* • *How were the results expressed? For binary outcomes, were relative and absolute effects reported?* • *Were the results reported for each outcome in each study group at each follow-up interval?* • *Was there any missing or incomplete data?* • *Was there differential drop-out between the study groups that could affect the results?* • *Were potential sources of bias identified?* • *Which statistical tests were used?* • *Were p values reported?*	
8. Was the precision of the estimate of the intervention or treatment effect reported? • Confidence intervals reported	Yes **X** No Can't Tell
CONSIDER: • *Were confidence intervals (CIs) reported?*	

9. Do the benefits of the experimental intervention outweigh the harms and costs? • A clear beneficial effect is continued for the group that was converted to sirolimus after 5 years • 74 serious adverse events did occur in 64 of the patients that were on sirolimus after first two years – this reduced to 36 in 43 of the patients in-between 2-5 years	Yes No Can't Tell **X**
CONSIDER: • *What was the size of the intervention or treatment effect?* • *Were harms or unintended effects reported for each study group?* • *Was a cost-effectiveness analysis undertaken? (Cost-effectiveness analysis allows a comparison to be made between different interventions used in the care of the same condition or problem.)*	
Section D: Will the results help locally?	
10. Can the results be applied to your local population/in your context? • Study population like that in local area, but smaller population • Important outcomes within population, as majority of patients on a CNI medication • Drug related problems noted and adverse reactions	Yes **X** No Can't Tell
CONSIDER: • *Are the study participants similar to the people in your care?* • *Would any differences between your population and the study participants alter the outcomes reported in the study?* • *Are the outcomes important to your population?* • *Are there any outcomes you would have wanted information on that have not been studied or reported?* • *Are there any limitations of the study that would affect your decision?*	
11. Would the experimental intervention provide greater value to the people in your care than any of the existing interventions?	Yes No Can't Tell **X**
CONSIDER: • *What resources are needed to introduce this intervention taking into account time, finances, and skills development or training needs?* • *Are you able to disinvest resources in one or more existing interventions in order to be able to re-invest in the new intervention?*	

3.2 Cohort Studies (Prospective study)

Reviewer Name:	Amber Sullivan
Paper Title:	Use of sirolimus as an adjuvant therapy for kidney transplant recipients with high-risk cutaneous squamous cell carcinomas: a prospective non-randomized controlled study.
Author:	Fázio et al. (2023)
Web Link:	https://www.scielo.br/j/jbn/a/sFWTqnRQfgNVXgBp4gXjvKk/?lang=en
Appraisal Date:	20th August 2025

Section A: Are the results valid?

1. Did the study address a clearly focused issue? KTRs are at high risk of SCC, specifically regarding certain immunosuppression use. This study looks at whether converting patients to sirolimus from CNI medication will improve SCC prognosis. Most importantly would it help those patients already at high risk of SCC.	Yes **X** No Can't Tell
CONSIDER: *A question can be 'focused' in terms of* • *the population studied* • *the risk factors studied* • *is it clear whether the study tried to detect a beneficial or harmful effect* • *the outcomes considered*	
2. Was the cohort recruited in an acceptable way? • Potential selection bias as groups non-randomised and some participants refused • Cohort needed to have already have or be high suspectable of SCC to be included in study	Yes No Can't Tell **X**
CONSIDER: • *Look for selection bias which might compromise the generalisability of the findings:* • *was the cohort representative of a defined population* • *was there something special about the cohort* • *was everybody included who should have been*	
3. Was the exposure accurately measured to minimise bias? • Blood tests completed for concentrations	Yes **X** No Can't Tell
CONSIDER: *Look for measurement or classification bias:* • *did they use subjective or objective measurements* • *do the measurements truly reflect what you want them to (have they been validated)* • *were all the subjects classified into exposure groups using the same procedure*	
4. Was the outcome accurately measured to minimise bias? • Reviewed by a nephrologist and lab work • New lesions were biopsied	Yes **X** No Can't Tell
CONSIDER: *Look for measurement or classification bias:* • *did they use subjective or objective measurements* • *do the measurements truly reflect what you want them to (have they been validated)* • *has a reliable system been established for detecting all the cases (for measuring disease occurrence)* • *were the measurement methods similar in the different groups* • *were the subjects and/or the outcome assessor blinded to exposure (does this matter)*	
5. (a) Have the authors identified all important confounding factors? Confounding factors: gender, age, dialysis information, transplant information, immunosuppressive regimen, skin type fitzpatrick scale	Yes **X** No Can't Tell
CONSIDER: • *list the ones you think might be important, and ones the author missed*	
b) Have they taken account of the confounding factors in the design and/or analysis? • Descriptive analysis	Yes No **X** Can't Tell
CONSIDER:	

• *look for restriction in design, and techniques e.g. modelling, stratified-, regression-, or sensitivity analysis to correct, control or adjust for confounding factors*	
6. a) Was the follow up of subjects complete enough? • High number of participants lost in groups • 24% loss in the conversion to sirolimus group • 31% loss in the maintenance CNI group	Yes No Can't Tell **X**
CONSIDER: • *the persons that are lost to follow-up may have different outcomes than those available for assessment* • *in an open or dynamic cohort, was there anything special about the outcome of the people leaving, or the exposure of the people entering the cohort*	
b) Was the follow up of subjects long enough? • 3 years	Yes **X** No Can't Tell
CONSIDER: • *the good or bad effects should have had long enough to reveal themselves*	
Section B: What are the results?	
7. What are the results of this study? The conversion from CNI to sirolimus was shown to be effective, with a reduced rate of incidence in the high risk SCC patients	Yes **X** No Can't Tell
CONSIDER: • *what are the bottom line results* • *have they reported the rate or the proportion between the exposed/unexposed, the ratio/rate difference* • *how strong is the association between exposure and outcome (RR)* • *what is the absolute risk reduction (ARR)*	
8. How precise are the results? • No confidence intervals	Yes No Can't Tell **X**
CONSIDER: • *look for the range of the confidence intervals, if given*	
9. Do you believe the results? • Small sample size • Needed randomisation	Yes No Can't Tell **X**
CONSIDER: • *big effect is hard to ignore* • *can it be due to bias, chance or confounding* • *are the design and methods of this study sufficiently flawed to make the results unreliable* • *Bradford Hills criteria (e.g. time sequence, dose-response gradient, biological plausibility, consistency)*	
Section C: Will the results help locally?	
10. Can the results be applied to the local population?	Yes No Can't Tell **X**
CONSIDER: • *Is a cohort study the appropriate method to answer this question* • *If the subjects covered in this study could be sufficiently different from your population to cause concern* • *If your local setting is likely to differ much from that of the study*	

• *If you can quantify the local benefits and harms*	
11.Do the results of this study fit with other available evidence?	Yes **X** No Can't Tell
12.What are the implications of this study for practice? • Similarities in other evidence, however small sample size and high loss to follow-up • Needs randomisation	Yes **X** No Can't Tell
CONSIDER: • *one observational study rarely provides sufficiently robust evidence to recommend changes to clinical practice or within health policy decision making* • *for certain questions, observational studies provide the only evidence* • *recommendations from observational studies are always stronger when supported by other evidence*	

3.3 For Cohort Studies (Retrospective study)

Reviewer Name:	Amber Sullivan
Paper Title:	Immunosuppression with mammalian target of rapamycin inhibitor and incidence of post-transplant cancer in kidney transplant recipients.
Author:	Opelz, G., Unterrainer, C., Süsal, C., & Döhler, B. (2016).
Web Link:	https://academic.oup.com/ndt/article/31/8/1360/1752177
Appraisal Date:	9th August 2025

Section A: Are the results valid?	
1. Did the study address a clearly focused issue? The risks of de novo mTOR inhibitor immunosuppression and those not on mTOR therapy and the direct link to cancer risks after KTRs	Yes **X** No Can't Tell
CONSIDER: *A question can be 'focused' in terms of* • *the population studied* • *the risk factors studied* • *is it clear whether the study tried to detect a beneficial or harmful effect* • *the outcomes considered*	
2. Was the cohort recruited in an acceptable way? • Data retrieved between 1999-2013 that meet inclusion criteria • Data requested from the transplant centre for the included participants – data provided over 3, 6 and 12 months post-transplant and then annually	Yes **X** No Can't Tell
CONSIDER: • *Look for selection bias which might compromise the generalisability of the findings:* • *was the cohort representative of a defined population* • *was there something special about the cohort* • *was everybody included who should have been*	
3. Was the exposure accurately measured to minimise bias? • Registry data • Working in collaboration with Collaborative transplant study (CTS) for the collection of information	Yes **X** No Can't Tell
CONSIDER: *Look for measurement or classification bias:*	

• *did they use subjective or objective measurements* • *do the measurements truly reflect what you want them to (have they been validated)* • *were all the subjects classified into exposure groups using the same procedure*	
4. Was the outcome accurately measured to minimise bias? • Data – for completeness and to avoid under-reporting, each transplant centre was requested to provide annual confirmation regarding completeness and accuracy • Coded using standard ICD 10 classification (C00-C96)	Yes **X** No Can't Tell
CONSIDER: *Look for measurement or classification bias:* • *did they use subjective or objective measurements* • *do the measurements truly reflect what you want them to (have they been validated)* • *has a reliable system been established for detecting all the cases (for measuring disease occurrence)* • *were the measurement methods similar in the different groups* • *were the subjects and/or the outcome assessor blinded to exposure (does this matter)*	
5. (a) Have the authors identified all important confounding factors? Cofounding factors: year of transplant, age, gender, ethnicity, underlying disease, initial immunosuppression	Yes **X** No Can't Tell
CONSIDER: • *list the ones you think might be important, and ones the author missed*	
b) Have they taken account of the confounding factors in the design and/or analysis? • Multivariable cox regression analysis	Yes **X** No Can't Tell
CONSIDER: • *look for restriction in design, and techniques e.g. modelling, stratified-, regression-, or sensitivity analysis to correct, control or adjust for confounding factors*	
6. a) Was the follow up of subjects complete enough? • No loss to follow up mentioned – use of registry data. Risks are reduced but not exempt	Yes No Can't Tell **X**
CONSIDER: • *the persons that are lost to follow-up may have different outcomes than those available for assessment* • *in an open or dynamic cohort, was there anything special about the outcome of the people leaving, or the exposure of the people entering the cohort*	
b) Was the follow up of subjects long enough? • Mean follow up 4.2 years	Yes **X** No Can't Tell
CONSIDER: • *the good or bad effects should have had long enough to reveal themselves*	
Section B: What are the results?	
7. What are the results of this study? • A reduced rate for the risks of NMSC in patients started on mTOR inhibitor from the initial time post-transplant • NMSC incidence lower in mTOR inhibitor group • Significant reduction for BCC and no effect for SCC	Yes **X** No Can't Tell

CONSIDER: • *what are the bottom line results* • *have they reported the rate or the proportion between the exposed/unexposed, the ratio/rate difference* • *how strong is the association between exposure and outcome (RR)* • *what is the absolute risk reduction (ARR)*	
8. How precise are the results? • Confidence intervals noted • Risk of BCC post-transplant 'markedly reduced (HR 0.56, 95%, CI 0.38-0.83) • Risk of SCC was not significantly reduced (HR 0.87; 95% CI 0.56-1.36	Yes **X** No Can't Tell
CONSIDER: • *look for the range of the confidence intervals, if given*	
9. Do you believe the results?	Yes **X** No Can't Tell
CONSIDER: • *big effect is hard to ignore* • *can it be due to bias, chance or confounding* • *are the design and methods of this study sufficiently flawed to make the results unreliable* • *Bradford Hills criteria (e.g. time sequence, dose-response gradient, biological plausibility, consistency)*	
Section C: Will the results help locally?	
10. Can the results be applied to the local population?	Yes **X** No Can't Tell
CONSIDER: • *Is a cohort study the appropriate method to answer this question* • *If the subjects covered in this study could be sufficiently different from your population to cause concern* • *If your local setting is likely to differ much from that of the study* • *If you can quantify the local benefits and harms*	
11.Do the results of this study fit with other available evidence?	Yes **X** No Can't Tell
12.What are the implications of this study for practice? • Risks of missing data as relying on previous records from several years • Unsure of loss to follow up – risk of selection bias • No information on drug regimens – risks of missing information necessary for the final data	Yes **X** No Can't Tell
CONSIDER: • *one observational study rarely provides sufficiently robust evidence to recommend changes to clinical practice or within health policy decision making* • *for certain questions, observational studies provide the only evidence* • *recommendations from observational studies are always stronger when supported by other evidence*	

Appendix 4: CASP checklist results (reduced format)

4.1 Cohort studies

Y = Yes, N = No, U = Can’t tell

Author	Q.1 Clarity of focus	Q.2 Suitability of cohort recruited	Q.3 Accuracy of exposure measured	Q.4 Accuracy of outcome measured	Q.5 Confounding factors	Q.6 Follow up of subjects	Q.7 What are the results	Q.8 Result precision	Q.9 Believability of results	Q.10 Application to local population	Q.11 Support ongoing evidence	Q.12 Implications for practice	Score
Alves et al. (2024)	Y	Y	Y	Y	a. Y b. U	a. Y b. Y	Y	N	?	Y	Y	Y	11/14
Ascha et al. (2017)	Y	Y	Y	Y	a. N b. Y	a. Y b. Y	Y	Y	Y	Y	Y	Y	13/14
Borlinić et al. (2017)	Y	Y	Y	Y	a. Y b. N	a. U b. Y	Y	N	U	Y	Y	Y	10/14
Bottomley et al. (2016)	Y	U	Y	Y	a. Y b. Y	a. Y b. U	Y	U	U	U	Y	U	8/14
Burke et al. (2015)	Y	Y	Y	Y	a. Y b. N	a. N b. U	Y	U	U	U	Y	Y	8/14
Cegielska et al. (2018)	Y	U	Y	Y	a. N b. N	a. U b. Y	Y	U	U	N	Y	Y	7/14
Crespo et al. (2017)	Y	U	Y	Y	a. N b. Y	a. N b. N	Y	U	U	U	Y	Y	7/14
Ducroux et al. (2017)	Y	Y	Y	Y	a. Y b. Y	a. Y b. Y	Y	N	U	Y	Y	Y	12/14
Fattouh et al. (2017)	Y	Y	Y	Y	a. Y b. U	a. N b. Y	Y	Y	Y	Y	Y	Y	12/14
Fázio et al. (2023)	Y	U	Y	Y	a. Y b. N	a. U b. Y	Y	U	U	U	Y	Y	8/14
Fuhrmann et al. (2022)	Y	U	Y	Y	a. Y b. Y	a. Y b. Y	Y	U	U	Y	Y	Y	11/14
Hayashida et al. (2015)	Y	Y	Y	Y	a. Y b. N	a. Y b. Y	Y	N	U	Y	Y	Y	11/14
Kaufmann et al. (2016)	Y	Y	Y	Y	a. Y b. Y	a. Y b. Y	Y	Y	Y	Y	Y	Y	14/14

Krásová et al. (2016)	Y	Y	Y	Y	a. N b. N	a. U b. Y	Y	Y	U	Y	Y	Y	11/14
Leonhard et al. (2023)	Y	Y	Y	Y	a. Y b. Y	a. U b. Y	Y	?	Y	U	Y	Y	11/14
Malagón-Liceaga et al. (2024)	Y	Y	U	Y	a. N b. Y	a. U b. Y	Y	Y	Y	Y	Y	Y	11/14
Murray et al. (2020)	Y	Y	Y	Y	a. Y b. Y	a. U b. U	Y	U	Y	Y	Y	Y	11/14
Musalem and Sáez-Vera (2025)	Y	Y	Y	U	a. Y b. N	a. U b. Y	Y	U	U	Y	Y	Y	9/14
Okut et al. (2017)	Y	Y	Y	Y	a. N b. N	a. Y b. Y	Y	U	U	Y	Y	Y	10/14
Opelz et al. (2016)	Y	Y	Y	Y	a. Y b. Y	a. U b. Y	Y	Y	Y	Y	Y	Y	13/14
Pinho et al (2016)	Y	U	Y	Y	a. Y b. Y	a. U b. Y	Y	U	Y	Y	Y	Y	11/14
Sachedina et al. (2024)	Y	Y	U	U	a. Y b. Y	a. Y b. Y	Y	Y	Y	U	Y	Y	11/14
Shao et al. (2022)	Y	Y	Y	Y	a. Y b. Y	a. Y b. Y	Y	Y	Y	Y	Y	Y	14/14
Shope et al. (2023)	Y	Y	Y	U	a. Y b. Y	a. Y b. Y	Y	U	Y	Y	Y	Y	12/14
Sułowicz et al. (2017)	Y	U	U	Y	a. U b. N	a. U b. Y	Y	U	U	Y	Y	Y	7/14
Thet et al. (2024)	Y	Y	U	Y	a. Y b. Y	a. Y b. Y	Y	Y	Y	Y	Y	Y	13/14

4.2 RCTs

Y = Yes, N = No, U = Can't tell

Author	Q1 Clear and well-formed question	Q2 Randomised participants	Q3 Loss to follow up accounted for (if any)	Q4 Blinded to intervention	Q5 Similarities of participants	Q6 Equal treatment	Q7 Comprehensive report	Q8 Precision of estimates	Q9 Benefits outweigh any implication	Q10 Ability to apply to local population	Q11 Use of intervention	Score
Dantal et al. (2018)	Y	U	Y	a. N b. N c. N	Y	Y	Y	Y	U	Y	U	7/11
Lim et al. (2017)	Y	Y	Y	a. Y b. U c. U	Y	Y	Y	Y	U	U	U	8/11
Ying et al. (2018)	Y	Y	Y	a. Y b. U c. U	Y	Y	Y	Y	Y	U	U	9/11