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Article type : Report



**Article type:** Original article

**mTOR inhibitors and skin cancer risk in non-renal solid organ transplant recipients: systematic review and meta-analysis**

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Running head: mTOR inhibitors in non-renal transplants

**Funding sources:** None.

**IRB approval status:** N/A

**PROSPERO Database:** N /A

**Conflicts of Interest:** None to declare.

**Reprint requests:** Anousha Yazdabadi

**Word count:** 2314

Abstract word count: 194

Capsule summary word count: 24

References: 37

Figures: 3

Tables: 1

Supplementary Figures: 0

Supplementary Tables: 1

## Abstract

**Background:** Solid organ transplant recipients have an increased risk of malignancy compared with the general population. mTOR inhibitors have been used as immunosuppressants in transplant recipients. There remains a lack of evidence of this treatment in non-renal solid organ transplantation. We aimed to perform a systematic review and meta-analysis to assess the effects of mTOR inhibitors on secondary NMSC malignancies in non-renal transplant recipients.

**Methods:** A systematic review and meta-analysis was performed according to PRISMA guidelines. Eligible studies for the present systematic review and meta-analysis included those in which patient cohorts underwent heart, liver, lung, pancreas (i.e. non-renal solid organ) transplantation, with treatment group being those treated with an mTOR inhibitor such as sirolimus or everolimus, and control group being placebo, or alternative non-mTOR inhibitor treatment such as calcineurin inhibitors or as per standard treatment protocol.

**Results:** From the 6 included studies, we found no significant difference in the odds of either primary or secondary NMSC (OR 0.73, 95% CI 0.41-1.29, P=0.28). Pooled analysis of patients with secondary NMSC demonstrated a trend towards significant benefit with mTOR inhibitor treatment (OR 0.61, 95% CI 0.37-1.02, P=0.06), but no protective effect for primary NMSC (OR 0.53, 95% CI 0.03-9.96, P=0.67).

**Conclusions:** Our results suggest that in non-renal transplant recipients, mTOR inhibitors may have a protective effect against secondary NMSC but not primary NMSC post-transplantation. Extrapolating the findings of reduced NMSC in renal transplant populations to non-renal transplant cases should be cautioned.

**Keywords:** mTOR; sirolimus; transplant; organ transplantation; skin cancer; basal cell carcinoma; squamous cell carcinoma

## Introduction

Solid organ transplant recipients have an increased risk of malignancy compared with the general population[1; 2]. The most common types of malignancy found in this population are non-melanoma skin cancers (NMSC), this includes squamous cell carcinomas (SCC), its precursors, as well as other NMSC such as basal cell carcinomas (BCC). Alarmingly, 60-80% of solid organ transplant recipients who develop a primary NMSC post-transplantation will develop a further primary NMSC within three years[3-5].

There has been increasing interest in one class of immunosuppressants, namely the mammalian target of rapamycin (mTOR) inhibitors which have reported anti-carcinogenic effects[6]. This is in contrast to other immunosuppressants such as mycophenolate or the calcineurin inhibitors cyclosporine, tacrolimus, and azathioprine, which can have pro-oncogenic effects [7-9]. The proposed mechanism of mTOR inhibitors is via the inactivation of the mTOR protein kinase, which therefore interferes with cell growth and proliferation, and hence slows down tumor growth and angiogenesis [10; 11].

Sirolimus and everolimus are mTOR inhibitors which have been used as immunosuppressants in transplant recipients. There is some long-term randomized evidence[12] and meta-analyses[13; 14] which have demonstrated that sirolimus is associated with reduced NMSC incidence in renal-transplant recipients, either as first-line therapy or when switched from calcineurin inhibitors due to primary NMSC post-transplant. On this note, it must be recognized that the risk of malignancies in solid organ transplantation is related to the level of immunosuppression, which is lower for kidney transplants compared to heart and lung organ transplantation[15-17]. There remains a lack of evidence on the effects of mTOR inhibitors on skin malignancies in non-renal solid organ transplantation.

To address current limitations in evidence, we performed a systematic review and meta-analysis to assess the effects of mTOR inhibitors on secondary NMSC malignancies in non-renal transplant recipients.

## Methods

### *Search strategy*

The present study was performed according to PRISMA guidelines and recommendations[18; 19]. Electronic searches were performed using Ovid Medline, PubMed, Cochrane Central Register of Controlled Trials (CCTR), Cochrane Database of Systematic Reviews (CDSR), ACP Journal Club, and Database of Abstracts of Review of Effectiveness (DARE) from their dates of inception to

19th July 2017. To achieve the maximum sensitivity of the search strategy, we combined the terms: “sirolimus”, “everolimus”, “transplant”, “mTOR”, “mammalian target of rapamycin”, “cutaneous cancer”, “cutaneous malignancy”, “squamous cell carcinoma”, “basal cell carcinoma”, as either key words or MeSH terms (Supplementary Table 1). The reference lists of all retrieved articles were reviewed for further identification of potentially relevant studies, assessed using the inclusion and exclusion criteria.

*Selection criteria*

Eligible studies for the present systematic review and meta-analysis included those in which patient cohorts underwent heart, liver, lung, pancreas (i.e. non-renal solid organ) transplantation, with treatment group being those treated with an mTOR inhibitor such as sirolimus or everolimus, and control group being placebo, or alternative non-mTOR inhibitor treatment such as calcineurin inhibitors or as per standard treatment protocol. For this systematic review, primary NMSC were defined as histologically confirmed NMSC which developed post-transplantation and secondary NMSC were defined as subsequent histologically confirmed non-recurrent non-metastatic NMSC which developed after the primary NMSC. Non-comparative studies, case series, case reports, abstracts, conference presentations, editorials, reviews and expert opinions were excluded as were studies that did not report the rate of new skin cancers. When institutions published duplicate studies with accumulating numbers of patients or increased lengths of follow-up, only the most complete reports were included for quantitative assessment at each time interval. All publications were limited to those involving human subjects.

*Data extraction and critical appraisal*

All data were extracted from article texts, tables and figures. Two investigators independently reviewed each retrieved article (K.P., A.Y.). Discrepancies between the two reviewers were resolved by discussion and consensus. The outcomes assessed included proportion of new skin cancers of any kind, proportion of new SCCs, and proportion of new BCCs.

*Statistical analysis*

The odds ratio (OR) was used as a summary statistic. In the present study, random-effect models were tested, where it was assumed that there were variations between studies. If studies reported hazard ratio, for the present study and for the purpose of pooling overall survival data, this was estimated to be equivalent to odds ratio[20; 21] for parameters with small number of events. $\chi^2$ tests were used to study heterogeneity between trials. $I^2$ statistic was used to estimate the percentage of total variation across studies, owing to heterogeneity rather than chance, with values greater than 50% considered as substantial heterogeneity. $I^2$ can be calculated as: $I^2 = 100\% \times (Q - df)/Q$, with Q defined as Cochrane’s heterogeneity statistics and df defined as degree of freedom. All P values were 2-sided. All statistical analysis was conducted

with Review Manager Version 5.3 (Cochrane Collaboration, Software Update, Oxford, United Kingdom).

## Results

*Search strategy*

A total of 554 studies were identified through multiple electronic database searches and from other sources such as reference lists (Supplementary Table 1 and Figure 1). After detailed assessment, 6 studies[22-27] remained for assessment. This comprised 436 non-renal transplant recipients in treatment group versus 839 non-renal transplant cases in the control (non-mTOR inhibitor) group (Table 1). Population characteristics are further detailed in Table 2.

*Study characteristics*

From the 6 included studies, 3 studies[22; 25-27] focused on the cardiac transplantation population, and 2 studies[23; 24] included a mix of transplant cases including lung, heart, liver and pancreas, and 1 study on liver transplants[27]. In terms of treatment, 3 studies[23-25] used sirolimus, 1 study[26] used everolimus, and 2 studies[22; 27] used a mix of sirolimus and everolimus. The comparator group included a mix of calcineurin inhibitors, mycophenylate mofetil, azathioprine and other immunosuppressive regimens. The size of the comparative studies varied from 30 patients[22] to 454 patients[26]. The average/median follow-up ranged from 3 years to 9.2 years. In terms of skin cancer types reported, 4 studies[22; 23; 25; 27] focused on secondary NMSC compared to 2 studies[24; 26] which focused on primary NMSC. For cutaneous malignancies, the most common reported type was SCC, followed by BCC, although this stratification was not reported by most studies.

*Effect of mTOR inhibitors on NMSC*

All 6 studies reported either the proportion of primary or secondary NMSC in treatment versus control groups. After pooled meta-analysis, we found no significant difference in the odds of either primary or secondary NMSC (OR 0.73, 95% CI 0.41-1.29, $I^2$=37%, P=0.28), without significant heterogeneity (Figure 2).

Subgroup analysis was performed to differentiate outcomes between rates of primary NMSC versus secondary NMSC post-transplant. Pooled analysis of patients with secondary NMSC demonstrated a trend towards significant benefit with mTOR inhibitor treatment (OR 0.61, 95% CI 0.37-1.02, $I^2$=0%, P=0.06), however this did not reach statistical significance. In terms of primary NMSC, no protective effect was observed (OR 0.53, 95% CI 0.03-9.96, $I^2$=79%, P=0.67).

Subgroup analysis was performed to determine effect of mTOR inhibitor treatment on rate of new SCCs, regardless of primary or secondary NMSC. From Figure 3, no significant difference was found in rate of new SCCs (OR 0.52, 95% CI 0.04-7.19, $I^2$=84%, P=0.63), with significant heterogeneity. Inadequate data was available from published literature to differentiate between primary versus secondary SCC.

The effect of mTOR inhibitors on rate of primary or secondary BCCs was also pooled. No significant difference was found in the rate of new BCCs (OR 1.41, 95% CI 0.63-3.18, $I^2$=0%, P=0.41), with no significant heterogeneity. Inadequate data was available from published literature to differentiate between primary versus secondary BCC.

## Discussion

To our knowledge, this is the first meta-analysis exploring the effect of mTOR inhibitors on NMSC in non-renal solid organ transplant recipients. Prior randomized trials and meta-analyses have focused on the role of mTOR inhibitors and risk of malignancies in renal transplant cases, which limits generalizability of their findings. In contrast to the renal transplant population, our meta-analysis demonstrates no significant association between sirolimus/everolimus use in preventing primary NMSC post non-renal transplant. We speculate that it may potentially have a protective effect against secondary NMSC post-transplantation, however the current available evidence does not support a significant effect.

Prior to the introduction of sirolimus, organ transplantation immunosuppression was predominantly based on the use of calcineurin inhibitors, steroids, cyclosporine and azathioprine. The majority of evidence has focused on the renal transplantation population. The success of sirolimus in phase II and III clinical trials[28] led to the FDA approval of sirolimus in combination with cyclosporine and steroids for kidney transplantation in 1999. Later studies including those of Mota and colleagues[29] demonstrated that renal histology improved after cyclosporine was withdrawn from the above regimen, leading to FDA approval of sirolimus for therapy without cyclosporine.

mTOR inhibitors target and inactivate the mTOR protein kinase. In doing so, it inhibits the mTOR pathway which inhibits cell growth and proliferation and can suppress the immune response[10]. Via these mechanisms, mTOR inhibitors can slow tumor growth and reduce angiogenesis associated with malignancies, resulting in an anti-carcinogenic effect. It also inhibits human herpes virus HHV-8 replication. As such, mTOR inhibitors can treat cancers such as renal cell carcinoma, Kaposi sarcoma, and BCCs[30; 31].

Few studies have focused on mTOR inhibitors and malignancies in non-renal transplant populations. Despite the large number of randomized studies performed in renal-transplant populations, it is unclear whether these can be extrapolated to non-renal transplant cases. Heart and lung transplant recipients are likely to receive higher levels of immunosuppression compared to kidney transplant recipients[17]. As such, these regimens are more likely to have higher tumorigenic potential[32]. There are also inherent differences in the clinical characteristics of different solid organ transplant populations. Heart transplant recipients had a mean proportion of 78.6% males compared to kidney (65.6%), lung (50.8%) and liver (55.3%) transplant recipients[17]. The effect of sex-mismatch appears to influence outcome, associated

with significantly reduced graft survival in heart and kidney transplants but not liver transplants[33]. In the same Norwegian national database analysis, liver transplant recipients tended to be younger (mean age 43.6 years) compared to kidney (49 years), heart (48.8 years) and lung (50.8 years) transplant recipients. Lung transplantation rates increase with age, reportedly due to higher rates of transplantation for idiopathic pulmonary fibrosis [34].These clinical differences between the renal and non-renal transplant population may potentially impact cancer risk post-transplantation.

Our present meta-analysis supports the notion that sirolimus or everolimus are not associated with reduction in risk of primary NMSC post-transplantation. There is a suggestion that it may play a role in the prevention of secondary NMSC, however current data does not statistically support this. These findings are in keeping with prior studies. Karia and colleagues[23] performed a 9-year retrospective cohort study of 329 solid organ transplant cases and analyzed the effect of sirolimus versus non-sirolimus treatment in preventing secondary NMSC. When they performed subgroup analysis of only non-renal transplant cases, they found a trend towards reduction in the proportion of any new skin cancer (P=0.09), cutaneous squamous cell carcinoma (P=0.09) but not basal cell carcinoma (P=0.54). Asgari et al[35] reported results from a retrospective cohort of 3539 solid organ transplant recipients with a mixture of kidney, heart, lung and liver transplant recipients. Although this study was not included in our meta-analysis as no subgroup analysis according to transplant type was performed, sirolimus treatment of this mixed solid organ transplant cohort was not significantly associated with risk of new SCC (HR 1.18, 95% CI 0.84-1.16). Wang et al[26] analyzed heart transplant cases, of which 222 patients were treated with everolimus compared to 232 with mycophenolate mofetil. Although a significant reduction of all cancers was noted in the mTOR inhibitor group, the proportion of skin cancers was found to be comparable. Overall, pooled available literature does not demonstrate any protective effect for mTOR inhibitors on primary NMSC in non-renal solid organ transplant recipients.

The use of sirolimus in solid organ transplantation is not necessarily benign. A meta-analysis[14] based on individual patient level data of 5876 kidney allograft recipients from 21 randomized studies demonstrated a significantly increased risk of mortality compared with non-sirolimus immunosuppression. This finding was driven by increased cardiovascular deaths and infection-related deaths and was found to be true in both patients taking sirolimus as first-line therapy as well as after switching from a calcineurin based therapy. In contrast, results from the TUMORAPA randomized study by Dantal et al[12] reported 5-year follow-up findings, which did not show differences in death rates. In a randomized study by Euvrard and colleagues in renal transplant recipients, 23% of the sirolimus group had to discontinue treatment due to adverse effects, including edema, acneiform eruption, aphthous ulcers, and proteinuria. The potential

risk of adverse events should be balanced with the aggressive nature of post-transplant cutaneous malignancies, and as such the decision to switch therapy to an mTOR inhibitor should be done with considerable thought into the relative benefits and risks for the individual patient.

The present study is constrained by multiple limitations. All included studies in this meta-analysis were not randomized and thus were susceptible to selection bias and observer bias. Studies based on coded or registry data are susceptible to coding error or incomplete or missing data, which may skew findings. There is a possibility that some skin cancers may have been treated independently outside the hospital and may not have been captured by the database. Data used for meta-analysis were predominantly unadjusted, and thus confounders including prior history of skin malignancies and inherent propensity to develop cancers could not be adjusted for, which may undermine the current results. Short median follow-up is a further limitation that is acknowledged. Given that the median time to primary NMSC post-transplant may take up to and over 9 years[36], longer follow-up duration would be more ideal in capturing the true rate of primary and secondary NMSC. There was also significant heterogeneity in terms of solid organ transplant populations, the number and doses of immunosuppressants, and the duration of immunosuppression.

In conclusion, our meta-analysis did not demonstrate a statistically significant protective effect for mTOR inhibitors in in non-renal transplant recipients against primary or secondary NMSC post-transplantation. We found no differences in the rates of new SCCs or BCCs with the use of mTOR inhibitors. Given the lack of high quality evidence, further prospective studies are required to evaluate non-renal solid organ transplant recipients with regards to risk factors for developing skin cancers, specifically SCC and BCC risk in these populations.

Acknowledgements: None declared

Conflicts of interest: None declared

Funding: None declared

**Figure legends**

Figure 1. PRISMA flow chart of search strategy for the present systematic review and meta-analysis

Figure 2. Forest plot of pooled odds ratio for rate of NMSC in mTOR inhibitor treatment versus control groups for non-renal transplant recipients, with subgroup analysis according to prior primary versus secondary NMSC

Figure 3. Forest plot of pooled odds ratio for rate of squamous cell carcinomas (SCC) and basal cell carcinomas (BCC) in mTOR inhibitor treatment versus control groups for non-renal transplant recipients

## References


1 I. Penn. Post-transplant malignancy: the role of immunosuppression. *Drug Saf* 2000; 23: 101-113.

2 M. C. Webb, F. Compton, P. A. Andrews *et al.* Skin tumours posttransplantation: a retrospective analysis of 28 years' experience at a single centre. *Transplant Proc* 1997; 29: 828-830.

3 G. Tessari, L. Naldi, L. Boschiero *et al.* Incidence and clinical predictors of a subsequent nonmelanoma skin cancer in solid organ transplant recipients with a first nonmelanoma skin cancer: a multicenter cohort study. *Arch Dermatol* 2010; 146: 294-299.

4 H. C. Wisgerhof, J. R. Edelbroek, J. W. de Fijter *et al.* Subsequent squamous- and basal-cell carcinomas in kidney-transplant recipients after the first skin cancer: cumulative incidence and risk factors. *Transplantation* 2010; 89: 1231-1238.

5 S. Euvrard, J. Kanitakis, E. Decullier *et al.* Subsequent skin cancers in kidney and heart transplant recipients after the first squamous cell carcinoma. *Transplantation* 2006; 81: 1093-1100.

6 S. N. Sehgal. Sirolimus: its discovery, biological properties, and mechanism of action. *Transplant Proc* 2003; 35: 7S-14S.

7 K. M. Thoms, C. Kuschal, E. Oetjen *et al.* Cyclosporin A, but not everolimus, inhibits DNA repair mediated by calcineurin: implications for tumorigenesis under immunosuppression. *Exp Dermatol* 2011; 20: 232-236.

8 D. B. Yarosh, A. V. Pena, S. L. Nay *et al.* Calcineurin inhibitors decrease DNA repair and apoptosis in human keratinocytes following ultraviolet B irradiation. *J Invest Dermatol* 2005; 125: 1020-1025.

9 P. O'Donovan, C. M. Perrett, X. Zhang *et al.* Azathioprine and UVA light generate mutagenic oxidative DNA damage. *Science* 2005; 309: 1871-1874.

10 M. A. Bjornsti, P. J. Houghton. The TOR pathway: a target for cancer therapy. *Nat Rev Cancer* 2004; 4: 335-348.

11 R. A. Lee, S. Gabardi. Current trends in immunosuppressive therapies for renal transplant recipients. *Am J Health Syst Pharm* 2012; 69: 1961-1975.

12 J. Dantal, E. Morelon, L. Rostaing *et al.* Sirolimus for Secondary Prevention of Skin Cancer in Kidney Transplant Recipients: 5-Year Results. *J Clin Oncol* 2018: JCO2017766691.

13 E. L. Yanik, K. Siddiqui, E. A. Engels. Sirolimus effects on cancer incidence after kidney transplantation: a meta-analysis. *Cancer Medicine* 2015; 4: 1448-1459.

14 G. A. Knoll, M. B. Kokolo, R. Mallick *et al.* Effect of sirolimus on malignancy and survival after kidney transplantation: systematic review and meta-analysis of individual patient data. *The BMJ* 2014; 349: g6679.

15 C. S. Ong, A. M. Keogh, S. Kossard *et al.* Skin cancer in Australian heart transplant recipients. *J Am Acad Dermatol* 1999; 40: 27-34.

16 R. P. Carroll, H. M. Ramsay, A. A. Fryer *et al.* Incidence and prediction of nonmelanoma skin cancer post-renal transplantation: a prospective study in Queensland, Australia. *Am J Kidney Dis* 2003; 41: 676-683.

17 S. M. H. Rizvi, B. Aagnes, H. Holdaas *et al.* Long-term Change in the Risk of Skin Cancer After Organ Transplantation: A Population-Based Nationwide Cohort Study. *JAMA Dermatol* 2017; 153: 1270-1277.

18 D. Moher, A. Liberati, J. Tetzlaff *et al.* Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* 2009; 339: b2535.

19 K. Phan, D. H. Tian, C. Cao *et al.* Systematic review and meta-analysis: techniques and a guide for the academic surgeon. *Ann Cardiothorac Surg* 2015; 4: 112-122.

20 M. D. Edwardes, M. Baltzan. The generalization of the odds ratio, risk ratio and risk difference to r x k tables. *Stat Med* 2000; 19: 1901-1914.

21 F. N. Doubal, P. E. Hokke, J. M. Wardlaw. Retinal microvascular abnormalities and stroke: a systematic review. *J Neurol Neurosurg Psychiatry* 2009; 80: 158-165.

22 A. O. Doesch, S. Muller, M. Konstandin *et al.* Malignancies after heart transplantation: incidence, risk factors, and effects of calcineurin inhibitor withdrawal. *Transplant Proc* 2010; 42: 3694-3699.

23 P. S. Karia, J. R. Azzi, E. C. Heher *et al.* Association of Sirolimus Use With Risk for Skin Cancer in a Mixed-Organ Cohort of Solid-Organ Transplant Recipients With a History of Cancer. *JAMA Dermatol* 2016; 152: 533-540.

24 S. Rashtak, R. A. Dierkhising, W. K. Kremers *et al.* Incidence and risk factors for skin cancer following lung transplantation. *J Am Acad Dermatol* 2015; 72: 92-98.

25 R. Rivinius, M. Helmschrott, A. Ruhparwar *et al.* Analysis of malignancies in patients after heart transplantation with subsequent immunosuppressive therapy. *Drug Des Devel Ther* 2015; 9: 93-102.

26 Y. J. Wang, N. H. Chi, N. K. Chou *et al.* Malignancy After Heart Transplantation Under Everolimus Versus Mycophenolate Mofetil Immunosuppression. *Transplant Proc* 2016; 48: 969-973.

27 P. Funk-Debleds, E. Ducroux, O. Guillaud *et al.* Subsequent nonmelanoma skin cancers and impact of immunosuppression in liver transplant recipients. *Journal of the American Academy of Dermatology* 2018; 79: 84-91.

28 A. S. MacDonald. A worldwide, phase III, randomized, controlled, safety and efficacy study of a sirolimus/cyclosporine regimen for prevention of acute rejection in recipients of primary mismatched renal allografts. *Transplantation* 2001; 71: 271-280.

29 A. Mota, M. Arias, E. I. Taskinen *et al.* Sirolimus-based therapy following early cyclosporine withdrawal provides significantly improved renal histology and function at 3 years. *Am J Transplant* 2004; 4: 953-961.

30 G. Stallone, A. Schena, B. Infante *et al.* Sirolimus for Kaposi's sarcoma in renal-transplant recipients. *N Engl J Med* 2005; 352: 1317-1323.

31 G. Hudes, M. Carducci, P. Tomczak *et al.* Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. *N Engl J Med* 2007; 356: 2271-2281.

32 B. Durando, J. Reichel. The relative effects of different systemic immunosuppressives on skin cancer development in organ transplant patients. *Dermatol Ther* 2005; 18: 1-11.

33 F. Puoti, A. Ricci, A. Nanni-Costa *et al.* Organ transplantation and gender differences: a paradigmatic example of intertwining between biological and sociocultural determinants. *Biology of Sex Differences* 2016; 7: 35.

34 E. S. Weiss, C. A. Merlo, A. S. Shah. Impact of advanced age in lung transplantation: an analysis of United Network for Organ Sharing data. *J Am Coll Surg* 2009; 208: 400-409.

35 M. M. Asgari, S. T. Arron, E. M. Warton *et al.* Sirolimus use and risk of cutaneous squamous cell carcinoma (SCC) in solid organ transplant recipients (SOTRs). *J Am Acad Dermatol* 2015; 73: 444-450.

36 C. A. Harwood, D. Mesher, J. M. McGregor *et al.* A surveillance model for skin cancer in organ transplant recipients: a 22-year prospective study in an ethnically diverse population. *Am J Transplant* 2013; 13: 119-129.

| Author | Year | Study region | Transplant type | Type of NMSC reported | n(treatment) | n (control) | Treatment | Comparator |
|---|---|---|---|---|---|---|---|---|
| Doesch | 2010 | Germany | Heart | Secondary NMSC | 16 | 14 | Sirolimus /everolimus. Switched from CNI-based immunosuppression, duration not provided | calcineurin inhibitor |
| Funk-Debleds | 2018 | France | Liver | Secondary NMSC- All having post-transplant history of NMSC (BCC, SCC or Bowen's disease) | 23 | 75 | Sirolimus /everolimus. Switched from other immunosuppression regimen, including – cyclosporine, tacrolimus, MMF, azathioprine, steroids, monoclonal anti IL2R antibodies, polyclonal antibodies. Switched after primary NMSC in 88% of cases, after average 6.3 years | calcineurin inhibitor |
| Karia | 2016 | United States | Lung, Heart, Liver, multiple | Secondary NMSC- All having post-transplant history of cancer of any type (SCC, BCC, lung, B-cell lymphoma, prostate, renal, melanoma, thyroid, bladder, | 34 | 112 | Sirolimus. Switched from other therapy used before primary NMSC – including azathioprine, steroids, cyclosporine, MMF, tacrolimus, after median 3.5 years | non-sirolimus, including azathioprine, prednisone, cyclosporine, mycophenolate mofetil, tacrolimus |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | breast, colon, other) | | | | |
| Rashtak | 2015 | United States | Lung, Heart, Pancreas | Primary NMSC - No prior malignancy post-transplant | 37 | 129 | Sirolimus | non-sirolimus, including cyclosporine, azathioprine, mycophenolate mofetil |
| Rivinius | 2014 | Germany | Heart | Secondary NMSC- All having prior cutaneous malignancy post-transplant | 104 | 277 | Sirolimus – was initial therapy for transplants performed after 2003 at this institution. Before 2003, was switched from another regimen including – cyclosporine, azathioprine, MMF, tacrolimus | non-sirolimus, including calcineurin inhibitors, azathioprine, mycophenolate mofetil, steroids |
| Wang | 2016 | Taiwan | Heart | Primary NMSC - No prior malignancy post-transplant | 222 | 232 | Everolimus | mycophenolate mofetil |

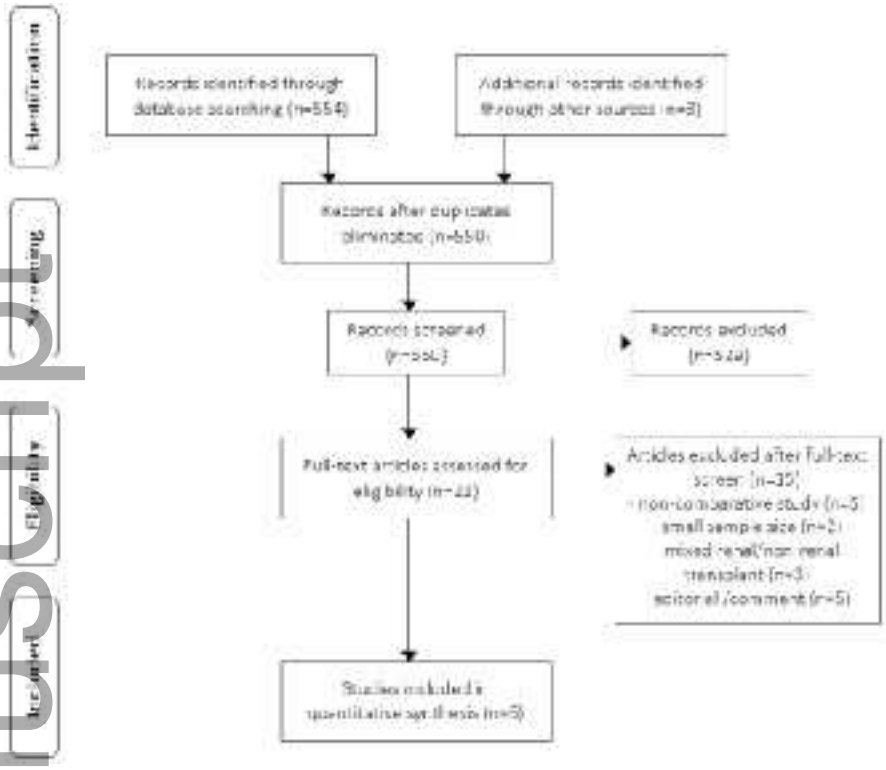
Table 1. Study characteristics. n, number of patients; MMF, mycophenolate mofetil

Table 2. Population description for each included study

| Author | Study population | Mean age at transplant (years) | Males (%) | Mean donor age (years) |
|---|---|---|---|---|

| | | | | |
|---|---|---|---|---|
| Doesch | Cardiac allograft recipients, where heart transplantation was performed from 1989 to 2005. All of these patients survived for more than 2 years after transplant and received induction therapy with antithymocyte globulin (RATG) guided by T-cell monitoring since 1994. | 51.4 ± 10.5 | 82.9 | 33.9 ± 16.2 |
| Funk-Debleds | Liver transplant recipients from 1987 to 2014. Reasons for transplantation includes alcoholic cirrhosis (52%), viral hepatitis C (11.2%), autoimmune liver disease (10.2%), and other. | 56.5 | 77.5 | - |
| Karia | Non renal transplant cases included lung, heart, liver, and multiple organs. | 58±13 for sirolimus group, 59±12 for no sirolimus group | 72.2% in sirolimus group, 68.5% in no sirolimus group | - |
| Rashtak | Lung transplant recipients from 1990-2011 at Mayo Clinic. 150 cases had lung transplantation alone, 15 cases had simultaneous heart and lung transplantation, 1 case had simultaneous heart, lung and liver transplantation. 8% with history of skin cancer. 12% with family history of skin cancer. | 52 ± 12 | 46 | - |
| Rivinius | Heart transplantation recipients at the University of Heidelberg, from 1989 to 2014. | 51.2 ± 10.5 | 46.9 | - |
| Wang | Pediatric heart transplantation cases, from the Pediatric Heart Transplant Study Database (international database with >36 centers contributing data), from 2004-2013. Only cases with at least 1 year follow-up were included. | 7.37±6.27 for sirolimus group, 6.79±6.23 for no sirolimus | 47.9 for sirolimus group, 54.3 for no sirolimus | - |

| | | | | |
|---|---|---|---|---|
| | | group | group | |

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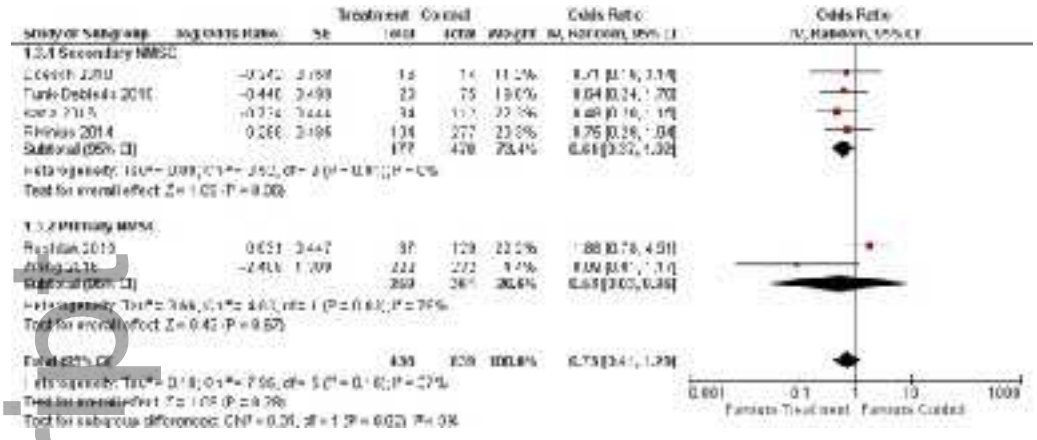


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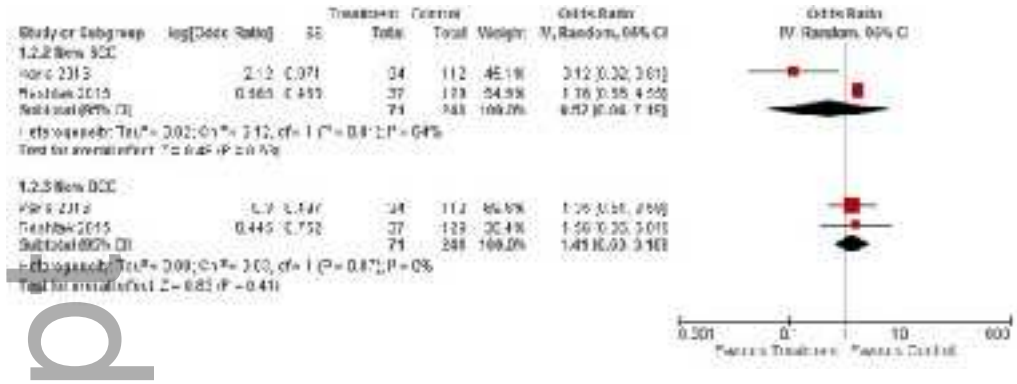

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