Incidence of nonmelanoma skin cancer in renal transplant recipients: A systematic review and meta-analysis

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INTRODUCTION

Renal transplantation has been considered the preferred treatment option regarding its positive impacts on patients’ life expectancy and quality of life.[1,2] The introduction of more potent immunosuppressive drugs has improved the outcome of renal transplantation. However, posttransplant malignancies can arise as a result of continuous exposure to immunosuppressive drugs.[3,4] Nonmelanoma skin cancer (NMSC), predominantly squamous cell carcinoma (SCC) and basal cell carcinoma (BCC), is one of the most malignancies following renal transplantation.[5,6]

A recent meta-analysis by Shang et al. has evaluated the cancer risk in patients receiving renal replacement therapy. The results of the meta-analysis indicated that there is an association between renal transplantation and an increased risk of NMSC.[7] Although the existing literature has provided relevant insights, some important questions remain to be answered. First of all, the estimate of the total incidence of NMSC among renal transplant recipients was 12.6% (95% CI: 12%–14%) with a majority of squamous cell carcinoma (SCC) 55% (95% CI: 47%–63%). The pooled estimate of the incidence rates of SCC and basal cell carcinoma was 2.7% (95% CI: 2%–3.4%) and 2.2% (95% CI: 1.5%–2.8%), respectively. Subgroup analysis per geographic location showed that pooled incidence of NMSC in renal transplant recipients was 39.1% (95% CI: 26.3%–51.8%), 12.4% (95% CI: 8.8%–16%), and 1.2% (95% CI: 0.4%–2%) in Australia and New Zealand, Europe, and Middle East, respectively. Conclusion: The results of the current meta-analysis demonstrated that the incidence of NMSC in renal transplant recipients varies widely. Regarding the high incidence of NMSC among renal transplant recipients, awareness of associated risk factors and early diagnosis of the malignancy in the population is a major clinical need.

Key words: Basal cell carcinoma, incidence, nonmelanoma skin cancer, renal transplantation, squamous cell carcinoma

How to cite this article: Matinfar M, Shahidi S, Feizi A. Incidence of nonmelanoma skin cancer in renal transplant recipients: A systematic review and meta-analysis. J Res Med Sci 2018;23:14.
totally and across different important subgroups (if data are available). We will also ascertain the incidence of SCC and BCC among this population which provides useful information for clinicians.

MATERIALS AND METHODS

Search strategy
A systematic search of literature was performed using a number of resources including PubMed, Medline, Scopus, and Web of Science databases. The search strategy included the following key terms: renal or kidney, transplant or transplantation or allograft, non-melanoma skin cancer or nonmelanoma skin cancer or NMSC. We did not apply any language or time restrictions, and the final search was conducted in February 2017. The reference list of all eligible articles was reviewed to detect further relevant articles.

Inclusion and exclusion criteria
The titles and abstracts of searched articles were reviewed by two independent authors (MM and SS). Studies were eligible if they meet the following inclusion criteria: (a) population-based studies on renal transplant recipients and (b) studies that provided incidence rate of NMSC or enough information to calculate incidence rates. The exclusion criteria were as follow: (a) studies on transplantation of organs other than kidney and (b) case reports, review articles, conference reports, and letters. If there were several publications on the same study, we used the most comprehensive one with the largest sample size or the longest follow-up time.

Data extraction and quality assessment
Two reviewers (MM and SS) independently performed data extraction, and any disagreements were picked up by a third author (AF). The following data were extracted from each study using standardized collection forms: first author, publication date, region, study design, sample size, sex, follow-up period, mean age at transplantation, number of NMSC, SCC, and BCC (where available), and incidence of NMSC, SCC, and BCC.

Two independent investigators assessed the quality of included studies. Investigators discussed their controversies and any disagreements were resolved through discussion and reevaluation.

Statistical analysis
To estimate the overall incidence and in subgroup meta-analyses, “metaprop program” in STATA version 14.0 (STATA, College Station, TX, USA) statistical software was used.[8] In this modeling approach, the incidence was estimated using pooling binomial data, and 95% confidence interval (CI) for incidence was constructed using score method.[9]

Heterogeneity was evaluated using the Cochran Chi-square test and the Cochrane-$I^2$ statistics as well as visual inspection of forest plot. Values of 25%, 50%, and 75% for $I^2$ were considered as low, medium, and high levels of heterogeneity, respectively.[10] Data were pooled using random effects model due to high levels of heterogeneity among included studies.[11] Possible sources of heterogeneity were explored by sensitivity and meta-regression, if possible, by subgroup analyses (based on geographic location and study design) and could be related to the duration of follow-up and mean age of participants.[12]

In current meta-analysis, publication bias was assessed by examining asymmetry in Begg funnel plots and conducting weighted Egger linear regression method, which suggested that the selection of publication was a likely source of bias. The sources of publication bias were also evaluated using sensitivity analysis, in which each individual study was removed from analyses.[13]

RESULTS

Search results
Twenty-nine eligible studies comprising a total of 36,021 renal transplant recipients were included in the current meta-analysis [Figure 1].[14-42] Of the 29 publications, 25 were used for estimating the incidence of NMSC[14-23,25-30,33-42] whereas 11 publications were included to estimate the incidence of SCC and BCC.[14,15,18,19,22,27,32,34,38,40,42] Basic characteristics of included studies are presented in Table 1.

Study characteristics
Majority of included studies had been performed in Europe ($n = 19$),[14,17,20,21,23,26,29,33,35,37,38,41] four in Australia and

![Figure 1: The flowchart of screened, excluded and analyzed studies](image-url)
### Table 1: Characteristics of included studies in the present meta-analysis

| Study               | Geographic origin | Kind of study | Sample size | Gender (male, %) | Mean age at transplantation | Number of patients with NMSC | Number of patients with SCC | Number of patients with BCC | Mean follow-up duration (year) | Time between transplantation and NMSC diagnosis (year) | Total number of NMSC | Number of SCC | Number of BCC |
|---------------------|-------------------|---------------|-------------|------------------|----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|---------------------------------|---------------------|-------------|--------------|
| Hartevelt et al. 1990 | Netherland        | Retrospective | 764         | 62               | NR*                        | 47                          | 25                          | 8                           | 8.7                         | 9.1                             | 176                  | 138         | 38           |
| Ramsay et al. 2000  | United Kingdom    | Prospective   | 182         | 67               | 37                         | 28                          | 3                           | 8                           | 7.6                         | NR                              | 114                  | 28          | 53           |
| Naldi et al. 2000   | Italy             | Retrospective | 1062        | 72.4             | NR                         | NR                          | NR                          | NR                          | NR                          | NR                              | NR                   | NR          | NR           |
| Harden et al. 2001  | United Kingdom    | Prospective   | 164         | NR               | 38.7                       | 15                          | NR                          | NR                          | 9.3                         | 8.9                             | NR                   | 41          | 28           |
| Ramsay et al. 2003  | Australia         | Prospective   | 361         | 60.4             | 40.2                       | 187                         | 135                         | 143                         | 7.56                        | NR                              | 3979                 | 1817        | 916          |
| Carroll et al. 2003 | Australia         | Prospective   | 310         | 61.2             | 41.82                      | 131                         | 89                          | 76                          | 1.5                         | NR                              | 850                  | 373         | 197          |
| Fuente et al. 2003  | Spain             | Prospective   | 174         | 67.8             | NR                         | NR                          | NR                          | NR                          | NR                          | NR                              | NR                   | NR          | NR           |
| Moloney et al. 2005 | Ireland           | Prospective   | 270         | 67.4             | NR                         | NR                          | NR                          | NR                          | NR                          | NR                              | NR                   | NR          | NR           |
| Moosa et al. 2005   | South Africa      | Retrospective | 542         | 54.2             | 37                         | NR                          | NR                          | 10                          | 7                           | 6.3                             | NR                   | NR          | NR           |
| Moloney et al. 2006 | Ireland           | Retrospective | 1558        | 64               | 40                         | 487                         | NR                          | NR                          | NR                          | NR                              | 28                   | 11          | 11           |
| Ramsay et al. 2007  | United Kingdom    | Prospective   | 244         | NR               | NR                         | NR                          | NR                          | NR                          | NR                          | NR                              | 28                   | 11          | 11           |
| Morellini et al. 2008 | Italy           | Retrospective | 400         | NR               | 48                         | NR                          | 12                          | NR                          | 2.83                        | 27                              | NR                   | NR          | NR           |
| Navarro et al. 2008 | Spain             | Prospective   | 1017        | NR               | NR                         | 50                          | NR                          | NR                          | 10                         | NR                              | NR                   | NR          | NR           |
| Comeau et al. 2008  | Canada            | Retrospective | 926         | 63.2             | NR                         | 44.7                        | 90                          | 27                          | 37                         | NR                              | 8.09                 | NR          | NR           |
| Mackenzie et al. 2009 | New Zealand     | Retrospective | 384         | 58.1             | NR                         | 41.5                        | 94                          | NR                          | 5.3                         | 18.3                            | NR                   | NR          | NR           |
| Kalinova et al. 2010 | Czech            | Retrospective | 603         | 61               | 47.4                       | 52                          | NR                          | NR                          | 5.5                         | 5.2                             | NR                   | NR          | NR           |
| Tessari et al. 2010 | Italy             | Retrospective | 1476        | 66               | NR                         | 44.4                        | 146                         | NR                          | 9.4                         | NR                              | NR                   | NR          | NR           |
| Keller et al. 2010  | Switzerland       | Prospective   | 243         | 63               | NR                         | NR                          | NR                          | NR                          | NR                          | NR                              | 158                  | 138         | 20           |
| Bretagnol et al. 2010 | France          | Retrospective | 1019        | 61.63            | NR                         | NR                          | NR                          | NR                          | NR                          | 6.5                             | NR                   | NR          | 42           |
| Zavos et al. 2011   | Greece            | Retrospective | 1736        | NR               | 46.3                       | NR                          | 39                          | NR                          | 7                           | 7.84                            | NR                   | NR          | NR           |
| Einollahi et al. 2012 | Iran              | Retrospective | 12525       | 63               | NR                         | 136                         | 39                          | 14                          | 1.83                        | 4.2                             | NR                   | NR          | NR           |
New Zealand,\cite{18,19,28,34} three in Middle East,\cite{36,40,42} and three in South Africa.\cite{22} Brazil,\cite{39} and Canada.\cite{27} There were 16 retrospective cohort studies,\cite{11,14,16,22,23,25,26,27,30,32,33,35,36,39,41,43} 12 prospective cohort studies.\cite{17,18,21,24,26,31,34,37,38,40} The mean age at transplantation and follow-up period ranged from 37 to 52.2 and 1.5 to 27.75 years, respectively. A total number of 1948 subjects developed NMSC in selected studies [Table 1].

**META-ANALYSIS AND QUANTITATIVE RESULTS**

The Cochran Q statistics ($P < 0.001$) and $I^2$ statistic indicated higher levels of heterogeneity ($I^2 > 90\%$) among included studies in meta-analysis for total incidence estimating as well as in all considered subgroup meta-analyses accordingly, all analyses were conducted in random-effect meta-analysis modeling approach.

The pooled incidence of NMSC was 12.6\% in renal transplant recipients (95\% CI: 11\%–14.2\%); however, the analysis showed significant heterogeneity across studies ($I^2 = 98.94$, $P < 0.001$) [Figure 2]. The sensitivity analysis indicated the exclusion of two studies\cite{12,13} led to a pooled estimate of 10\% (95\% CI: 8.6\%–11.4\%) ($I^2 = 98.69$, $P < 0.001$). The pooled estimate of the proportion of tumors revealed that 55\% (95\% CI: 47\%–63\%) ($I^2 = 96.72$, $P < 0.001$) and 36\% (95\% CI: 30\%–42\%) ($I^2 = 94.05$, $P < 0.001$) of all NMSCs were SCC and BCC, respectively [Figure 3a and b]. Our results also indicated that the pooled proportion of patients with SCC and BCC were 44\% (95\% CI: 30.9\%–57.2\%) ($I^2 = 94.11$, $P < 0.001$) and 38.3\% (95\% CI: 21\%–55.7\%) ($I^2 = 96.89$, $P < 0.001$), respectively [Figure 4a and b].

The pooled incidence rates of SCC and BCC were 2.7\% (95\% CI: 2\%–3.4\%) ($I^2 = 97.77$, $P < 0.001$) and 2.2\%
Matinfar, et al.: Non melanoma skin cancer incidence in renal transplant recipients

Journal of Research in Medical Sciences | 2018 |

5 (95% CI: 1.5%–2.8%) ($I^2 = 97.67$, $P < 0.001$) respectively [Figure 5a and b]. The sensitivity analysis revealed that omission of studies with the highest incidence rate[12,13] led to changes in estimated pooled incidence of 1.2% (95% CI: 0.8%–1.6%) ($F = 93.01, P < 0.001$) and 0.8% (95% CI: 0.5%–1.1%) ($F = 91.49, P < 0.001$) for SCC and BCC, respectively.

We performed a subgroup analysis to explore the incidence of NMSC among renal transplant recipients in various geographic regions. The results of subgroup analysis per geographic location indicated that pooled incidence of NMSC was 39.1% (95% CI: 26.3%–51.8%) ($F = 95.34, P < 0.001$), 12.4% (95% CI: 8.8%–16%) ($F = 98.49, P < 0.001$), and 1.2% (95% CI: 0.4%–2%) ($F = 96.48, P < 0.001$) in Australia and New Zealand, Europe, and Middle East, respectively [Figure 6].

The results of subgroup analysis based on the study design showed that pooled estimate for NMSC was 22% for prospective (95% CI: 15%–29%) ($F = 99.10, P < 0.001$), and 9% (95% CI: 7%–12%) ($F = 98.80, P < 0.001$) for retrospective studies [Figure 7].

Publication bias and sensitivity analysis and meta-regression

The funnel plots were used for examining the publication bias, no evidences were detected from the plots in one hand, and on the other hand, the results of both Begg’s rank correlation method and Egger weighted regression method suggested no statistically significant asymmetry in funnel plots. Trim and fill method also was used as a complementary approach to adjust the funnel plot asymmetry, but the results showed no trimming performed and data unchanged. The meta-regression analysis for evaluating the possible cofounding effects of mean age of participants and follow-up period of included studies showed no significant associations; in other word, they...
could not be considered as sources of heterogeneity. Furthermore, sensitivity analyses’ results showed no significant change in estimated overall incidence as well as its values in subgroup analyses in this meta-analysis after excluding studies that were considered lower quality.

DISCUSSION

Advances in kidney transplantation have improved both graft and patients’ survival. However, long-term exposure to immune suppressive drugs leads to chronic medical conditions such as posttransplant malignancies. The most frequent malignancy after renal transplantation is NMSC. Some factors are regarded to contribute to susceptibility for NMSC. Older age, male sex, fair skin type, ultraviolet (UV) exposure, and duration of immnosuppression are reported to be associated with the risk of NMSC in renal transplant patients.

The results of the present meta-analysis indicated that the incidence of NMSC in renal transplant patients was 12% with SCC as the most predominant tumor. It is estimated that BCC and SCC comprise about 80% and 20% of all NMSC in the general population. Conversely, in renal recipient patients, the majority of NMSC are SCC with a more aggressive phenotype, higher metastatic, and recurrence rate. However, this pattern has not been seen in all of studies which have assessed NMSC incidence after renal transplantation. The most common form of NMSC has been BCC in some studies done in Spain, Portugal, or Italy. Possibly, a number of factors such as genetic background, patterns of sun exposure, and skin type are among factors that change the ratio of BCC/SCC among renal transplant population. In addition, regarding the linear increase in BCC incidence after renal transplantation, possibly long-term follow-up studies detect the true difference between SCC and BCC incidence among this population.

The subgroup analysis conducted for geographic locations revealed that the incidence of NMSC in Australia is 39.1%. The assessment of NMSC in general population has also shown that the incidence of the malignancy varies widely across the world with the highest incidence in Australia. One possible reason for higher incidence of NMSC among renal transplant recipients in Australia and New Zealand is higher UV radiation intensity in the location. It is detected that southern hemisphere has a greater intensity of UV radiation which its clearer skies increase it to 15%. The low incidence of NMSC among Middle East population regarding the lack of highly pigmented (Fitzpatrick V and VI) skin types and exposure to high sunlight, casting some doubts on the role of sunlight exposure as the main determinant of high NMSC risk among Australians.
Previous studies have reported a potential association between the expression of some human leukocyte antigens and NMSC.\cite{54} It also supposed that lower incidence of NMSC in renal transplant recipients in the Middle East are explained by some ethnic variations such as wearing protective clothing and different sunbathing habits.\cite{54}

**CONCLUSION**

The results of the present meta-analysis indicated that the incidence of NMSC varies greatly in different populations. High heterogeneity was observed in various subgroups in the present meta-analysis indicating that there might be other factors such as clinical and environmental risk factors that need to be considered to explain differences in the incidence of NMSC among renal transplant recipients. Regarding the high incidence of NMSC among renal transplant recipients, awareness of associated risk factors and early diagnosis of the malignancy in the population is a major clinical need.

**Financial support and sponsorship**

Nil.

**Conflicts of interest**

There are no conflicts of interest.

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