Review Article

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

Mohammad Matinfar[1], Shahrzad Shahidi[1,2], Awat Feizi[3]

[1]Department of Internal Medicine, Division of Nephrology, Isfahan University of Medical Sciences, [2]Isfahan Kidney Diseases Research Center, Isfahan University of Medical Sciences, [3]Isfahan Endocrine and Metabolism Research Center and Department of Biostatistics and Epidemiology, School of Health, Isfahan University of Medical Sciences, Isfahan, Iran

Background: Nonmelanoma skin cancer (NMSC) in renal transplant recipients is common and associated with significant morbidity and mortality. The aim of the present systematic review and meta-analysis was to estimate the incidence of NMSC among renal transplant recipients. **Materials and Methods:** We systematically searched PubMed, Medline, Scopus, and Web of Science databases for studies that assessed the incidence of NMSC in renal transplant recipients using a combination of relevant keywords. Two independent investigators included studies and extracted necessary information. Random effect meta-analysis was used to estimate pooled incidence of NMSC with 95% confidence intervals (CIs). **Results:** Twenty-nine studies comprising 36,021 patients meet the criteria for the systematic review. The pooled incidence of NMSC in 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 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

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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]

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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 as well as across subgroups for this high-risk population is remained unclear. In addition, the incidence of SCC and BCC as the most frequent skin cancers in renal transplant recipients has not been elucidated. Accordingly, the aim of the present systematic review and meta-analysis is to estimate the incidence of NMSC among renal transplant recipients

Address for correspondence: Dr. Shahrzad Shahidi, Kidney Diseases Research Center, Isfahan University of Medical Sciences, Isfahan, Iran. E-mail: shahidi@med.mui.ac.ir

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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

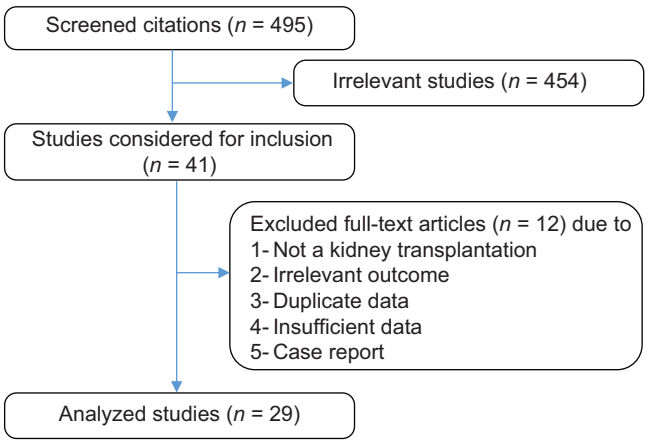

Figure 1: The flowchart of screened, excluded and analyzed studies

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	37.5	71	NR	NR	25.75	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	45	39	NR	NR	6	NR	NR	NR	NR
Moloney *et al*. 2005	Ireland	Prospective	270	67.4	NR	56	NR	NR	NR	NR	NR	NR	NR
Moosa *et al*. 2005	South Africa	Retrospective	542	54.2	37	10	5	7	6.3	NR	NR	NR	NR
Moloney *et al*. 2006	Ireland	Retrospective	1558	64	40	487	NR	NR	NR	NR	NR	NR	NR
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	12	NR	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	44.7	90	27	37	NR	8.09	NR	NR	NR
Mackenzie *et al*. 2009	New Zealand	Retrospective	384	58.1	41.5	94	NR	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	44.4	146	NR	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	44.3	NR	NR	NR	6.5	NR	NR	42	47
Zavos *et al*. 2011	Greece	Retrospective	1736	NR	46.3	39	25	7	NR	7.84	NR	NR	NR
Einollahi *et al*. 2012	Iran	Retrospective	12525	63	NR	136	39	14	1.83	4.2	NR	NR	NR

Contd...

Table 1: Contd...

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
Ng el al. 2014	Australia	Prospective	142	63	42.1	53	NR	NR	1.9	NR	341	253	88
Vrotniakaite *et al.* 2014	Lithuania	Retrospective	395	54.9	40.33	3	NR	NR	12	3.89	NR	NR	NR
Tepeoğlu *et al.* 2014	Turkey	Retrospective	1275	NR	38	33	10	9	NR	5.41	NR	NR	NR
Bernat-García *et al.* 2014	Spain	Prospective	289	NR	52.2	73	NR	NR	6	4.87	NR	NR	NR
Bannon *et al.* 2014	Ireland	Prospective	3507	62.5	41.6	NR	NR	NR	NR	NR	NR	NR	NR
Goncalves *et al.* 2015	Brazil	Retrospective	165	54.5	NR	11	NR	NR	6.06	3.14	19	10	9
Keles *et al.* 2015	Turkey	Prospective	4000	NR	NR	12	4	5	NR	5.1	NR	NR	NR
Pinho *et al.* 2016	Portugal	Retrospective	288	66	47	71	30	27	NR	5.35	131	69	62

NR=Not reported; NMSC=Non-melanoma skin cancer; SCC=Squamous cell carcinoma; BCC=Basal cell carcinoma

New Zealand,[18,19,28,34] three in Middle East,[36,40,42] and three in South Africa,[22] Brazil,[39] and Canada.[27] There were 16 retrospective cohort studies,[14,16,22,23,25,27-30,32,33,35,36,39,41,42] 12 prospective cohort studies.[17-21,24,26,31,34,37,38,40] 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[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%

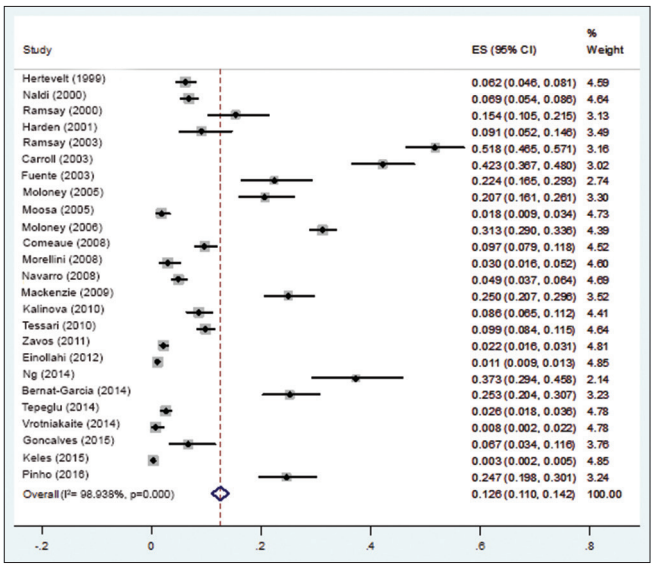

Figure 2: Forest plot for pooled estimate of incidence of nonmelanoma skin cancer incidence in renal transplant recipients

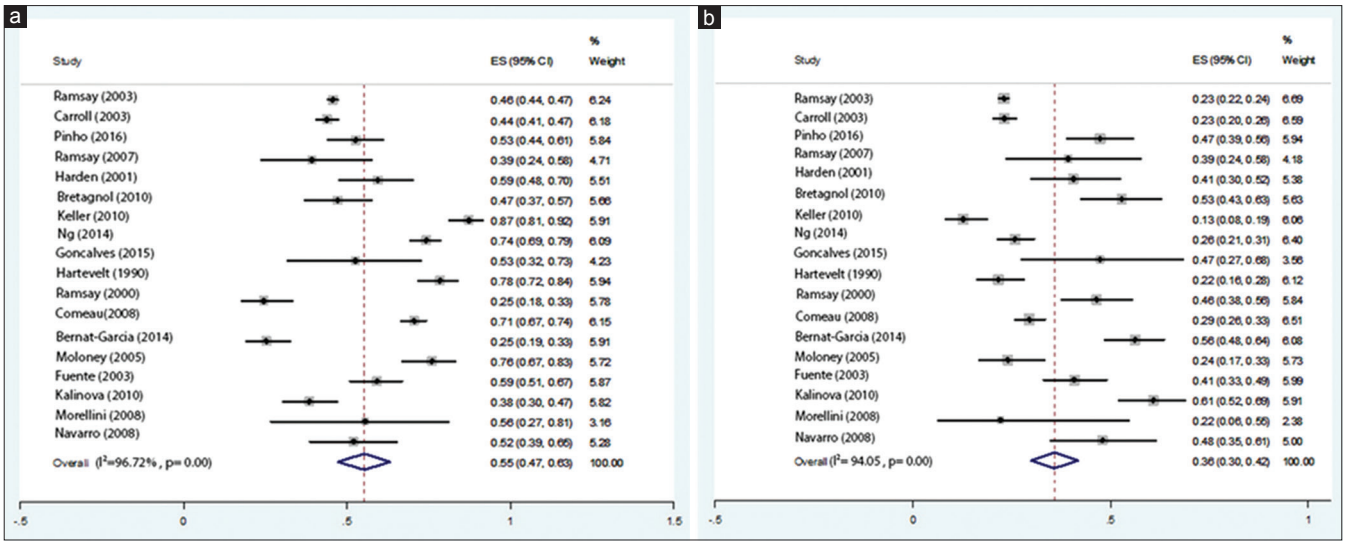

Figure 3: (a) Forest plot for pooled estimated proportion of squamous cell carcinoma tumors and (b) Forest plot for pooled estimated proportion of basal cell carcinoma tumors

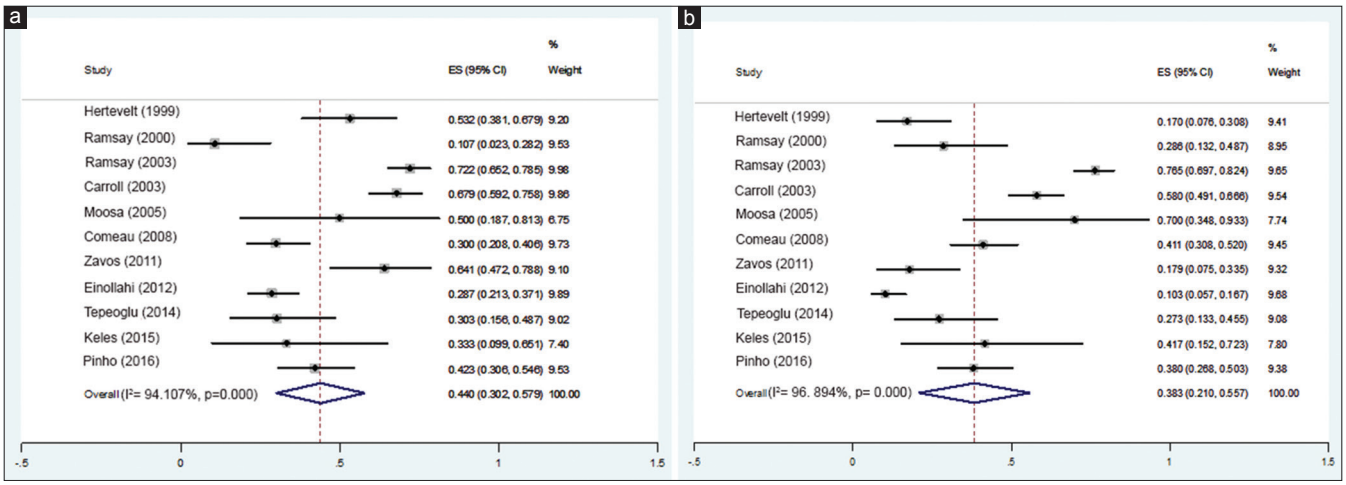

Figure 4: (a) Forest plot for pooled estimated proportion of patients with squamous cell carcinoma and (b) Forest plot for pooled estimated proportion of patients with basal cell carcinoma

(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%) (I^2 = 93.01, P < 0.001) and 0.8% (95% CI: 0.5%–1.1%) (I^2 = 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%) (I^2 = 95.34, P < 0.001), 12.4% (95% CI: 8.8%–16%) (I^2 = 98.49, P < 0.001), and 1.2% (95% CI: 0.4%–2%) (I^2 = 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%) (I^2 = 99.10, P < 0.001), and 9% (95% CI: 7%–12%) (I^2 = 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

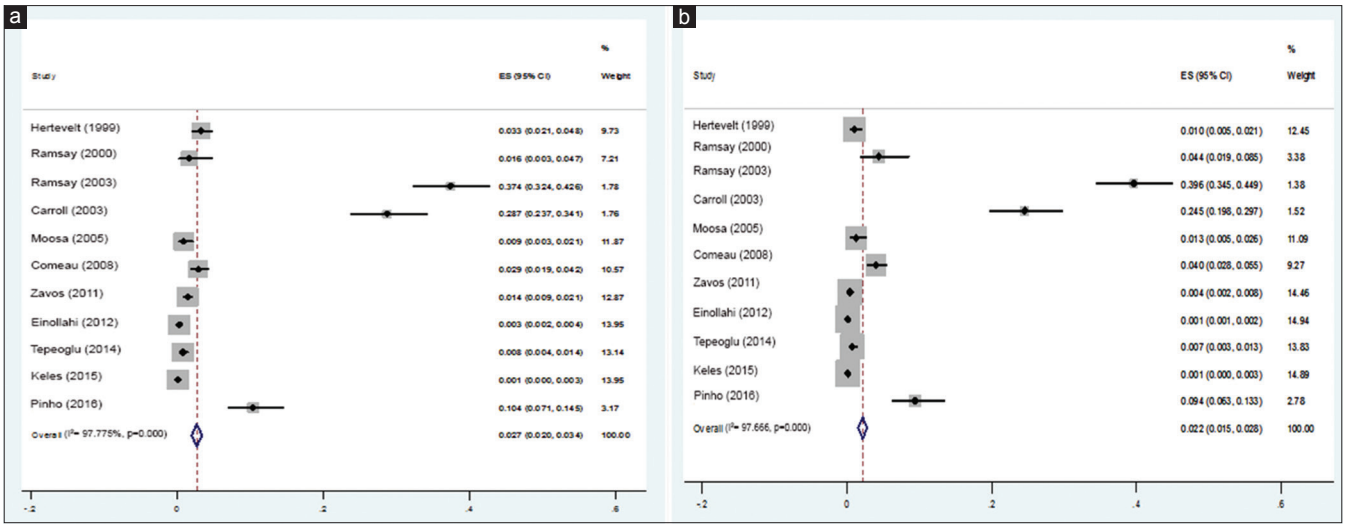

Figure 5: (a) Forest plot for pooled estimated incidence of squamous cell carcinoma and (b) Forest plot for pooled estimated incidence of basal cell carcinoma

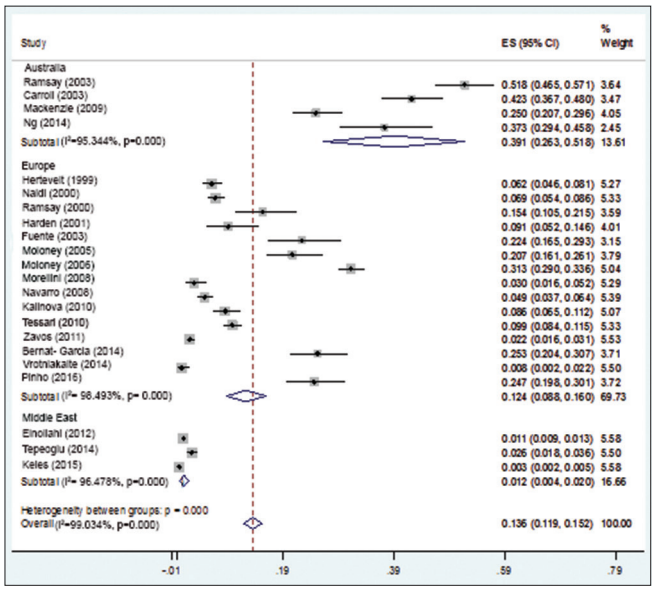

Figure 6: Forest plot of pooled estimated incidence of nonmelanoma skin cancer in subgroup analysis based on geographic location

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.[43-45] The most frequent malignancy after renal transplantation is NMSC.[46] Some factors are regarded to contribute to susceptibility for NMSC. Older age, male sex, fair skin type, ultraviolet (UV) exposure, and duration of immunosuppression are reported to be associated with the risk of NMSC in renal transplant patients.[15,19-21,24,27,39,41]

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.[47] 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.[16,20,41] 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.[48] 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%.[49,50] 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.

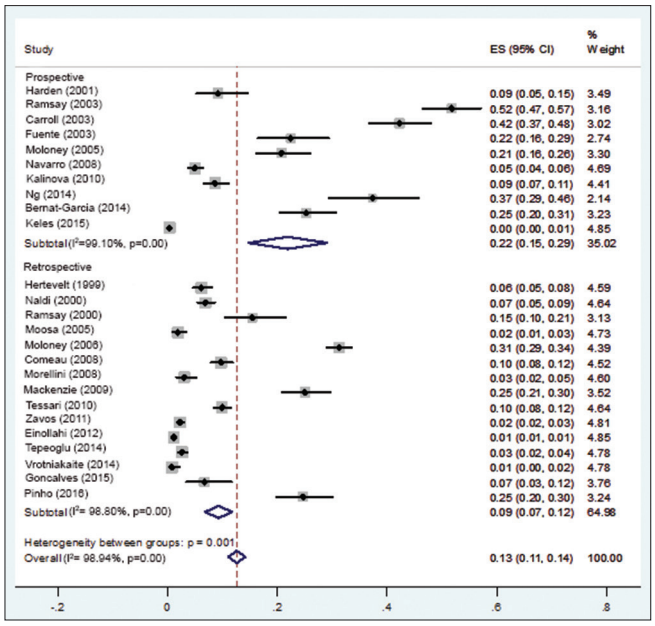

Figure 7: Forest plot of estimated incidence of nonmelanoma skin cancer in subgroup analysis based on study design

Previous studies have reported a potential association between the expression of some human leukocyte antigens and NMSC.[47,51-53] It also supposed that lower incidence of NMSC in renal transplant recipients in the Middle East are explained by some ethic variations such as wearing protective clothing and different sunbathing habits.[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.

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Conflicts of interest
There are no conflicts of interest.

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