Risk of Non-melanoma Skin Cancer in Kidney Transplantation Recipient: An Evidence-based Case Report

Riva Ambardina Pradita, Ayutika Saraswati Adisasmito, Wresti Indriatmi*

Department of Dermatology and Venereology, Faculty of Medicine Universitas Indonesia - Cipto Mangunkusumo Hospital, Jakarta, Indonesia.

Corresponding Author:
Riva Ambardina Pradita, MD. Department of Dermatology and Venereology, Faculty of Medicine Universitas Indonesia - Cipto Mangunkusumo Hospital. Jl. Pangeran Diponegoro no. 71, Jakarta 10430, Indonesia.
Email: ambardinapradita@gmail.com

ABSTRACT

Background: *Renal transplantation is the most common organ transplantation procedure in Indonesia. Renal transplant recipients (RTRs) were found to carry 3-to-5-time higher risk of cancer compared to the normal population. Around 40% of cancers in RTR patients were non-melanoma skin cancer (NMSC). It was found to be correlated with several risk factors. The study aimed to determine the prognostic factors for NMSC in RTRs with Indonesian skin colors.* ***Methods:*** *The article search was conducted on three different journal databases, which were Cochrane, PubMed, and Embase. Relevant articles were appraised using critical appraisal guidelines from The Centre for Evidence-Based Medicine (CEBM), University of Oxford.* ***Results:*** *Four articles were selected for appraisal. Incidence of NMSC on RTRs in these studies were 25,2% (CI 24,67%-32,47%), 6,67% (CI 2,87%-10,47%), 23,67% (CI 19,38%-27,96%) and 28,57% (CI 24,67%-32,47%). Prognostic factors correlated with the incidence of NMSC on RTRs were age, sun exposure, history of sunburn, existing chronic actinic lesion, lentigo solaris, precancerous lesion including actinic keratoses, and consumption of cyclosporine and tacrolimus during maintenance therapy.* ***Conclusion:*** *Combination of age, environmental factors, sun exposure-related skin lesion, and immunosuppressant therapy are the main prognostic factors of NMSC on RTRs.*

Keywords: *non-melanoma skin cancer, renal transplant recipient, renal transplantation*

INTRODUCTION

Each year, there are more than 69.400 kidney transplantations performed worldwide.[1] Renal transplantation is the most frequent transplantation procedure performed in Indonesia, almost 50% of which took place in Cipto Mangunkusumo Hospital (RSCM). From 2001 until 2020, as many as 810 renal transplantations had been successfully carried out in RSCM, with a one-year survival rate after transplantation reaching almost 90%.[2]

The survival of RTRs post-transplantation is mainly dependent on a variety of immunosuppressants consumed over a long period to avoid donor rejection. However, immunosuppressants increase the risk of carcinogenesis in RTRs by up to five times than it does in the normal population. Non-melanoma skin cancer (NMSC) makes up about 40% of all skin cancers in RTRs.[3,4] Squamous cell carcinoma (SCC), a subtype of NMSC, is more frequent in RTRs compared to the basal cell carcinoma (BCC) subtype. Meanwhile, the opposite is true for the normal population. Skin cancer in RTRs often develops within 5-10 years post-transplantation.[5] In comparison to the normal population, NMSC in RTRs is more likely to be aggressive, multiple in number,

and easier to metastasize.[4] Immunosuppressed condition in RTRs is thought to disturb tumor growth inhibitory mechanism due to a variety of carcinogens. In addition, the proliferation of oncogenic viruses is also difficult to control.[4] NMSC prevalence in RTRs is thought to be multifactorial. Aside from immunosuppression therapy, there are other prognostic factors contributing to the increase of NMSC risk in RTRs, among others, lighter skin color (FST < 3), older age, male gender, sun exposure, Human Leukocyte Antigen (HLA) mismatches, and presence of a chronic actinic lesion.[4]

Most of the studies concerning NMSC in RTRs were conducted on Caucasian population. Meanwhile, studies about NMSC in Asian RTRs are still scarce. This might be due to darker skin color being protective against NMSC in RTRs. However, a study in Singapore stated a prevalence of 4,7% of NMSC in RTRs, which was higher than the national prevalence of NMSC.[6] This was in concordance with other studies in South Korea and India, where NMSC's prevalence in RTRs reached 3.8%[7] and 3.12% respectively.[8]

Even though whiter skin phototype has been known as a strong risk factor of NMSC in RTRs, NMSC does not exclusively affect RTRs of fairer skin colour and may affect RTRs with darker skin shade. In addition, data regarding the incidence of NMSC in Indonesian RTR is scarce. Considering this information, we conducted this evidence-based case report to assess the risk factors associated with NMSC in an Indonesian patient.

CASE ILLUSTRATION

A 43-year-old Indonesian man, FST IV, was admitted to RSCM in September 2021, with a chief complaint of an asymptomatic mole that had been growing on his face for three months (**Figure 1**). He had undergone kidney transplantation seven years ago as he was diagnosed with end-stage kidney disease secondary to hypertension in 2013. Prior to receiving a kidney transplant, he had been regularly visiting the hospital for hemodialysis.

The transplanted kidney was functioning well, and the patient was maintained with immunosuppressive maintenance therapy consisting of tacrolimus and mycophenolate mofetil (MMF) for a lifetime. The patient was an office worker, spending most of the day indoors hence having low ultraviolet sunlight exposure. The patient had no history of smoking, radiation therapy, exposure to coal tar or arsenic, sexually transmitted diseases, sunburn, traumatic scars, or chronic skin irritation. There was no remarkable family history of skin disease or skin cancer.

METHODS

Article search was done via three databases: Cochrane, PubMed, and Embase, on 28 March 2021. Keywords used in the article search were filtered using medical subject headings (MeSH terms) and "text words" in the Title or Abstract. They were also connected with the Boolean operator. A critical review was done by the first and second authors as reviewers, based on the guideline for critical review for prognostic study from The Centre for Evidence-Based Medicine (CEBM), University of Oxford.

RESULTS

The results from article search in Cochrane, PubMed, and Embase are presented in **Figure 1** and **Table 1**. Based on the guideline from The Oxford Centre of Evidence-Based Medicine, in order to answer prognostic clinical question, systematic reviews and meta-analysis from cohort studies were determined to be most superior. However, we found no relevant and eligible study with those designs. This paper included four cohort study with a level of evidence 2b. The first article was written by Bernat et al[9], an ambidirectional cohort study. The other articles were written by Goncalves et al[10], Kaufmann et al[11], Zavattaro et al[12], and were all retrospective cohort studies. Study characteristics, critical review results, and the outcome of each study are presented in **Table 2, Table 3**, and **Table 4**.

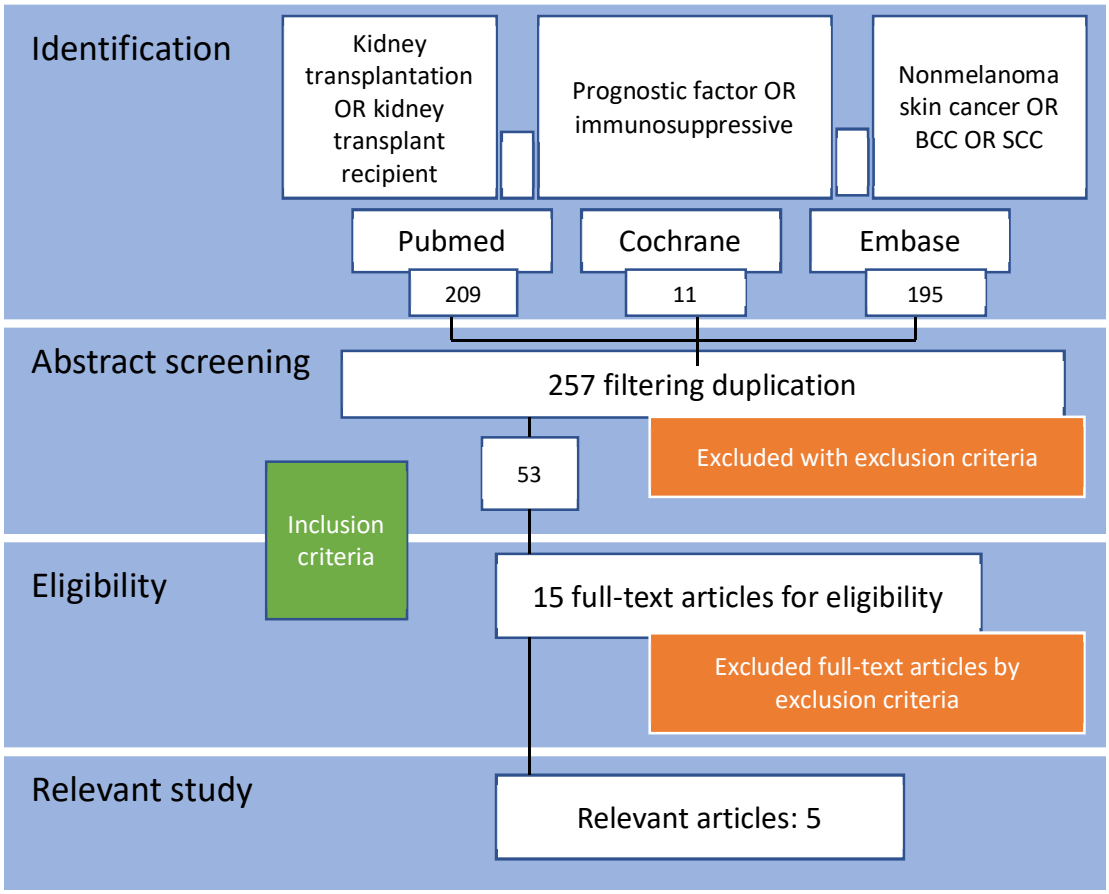

Figure 1. Search flowchart

Table 1. Article search result

Database	Keywords	Result
Cochrane	(("renal transplant recipient"):ti,ab,kw) OR (MeSH descriptor: [Kidney Transplantation])) AND ((MeSH descriptor: [Prognosis]) OR (MeSH descriptor: [Immunosuppression])) AND ((MeSH descriptor: [Skin Neoplasms]) OR (MeSH descriptor: [Neoplasms, Basal Cell]) OR (MeSH descriptor: [Neoplasms, Squamous Cell]) OR (("nonmelanoma skin cancer"):ti,ab,kw))	11
PubMed	renal transplantation"[Title/Abstract]) OR (kidney transplantation[Title/Abstract])) OR (renal transplantation recipient[Title/Abstract])) OR (kidney transplantation recipient[Title/Abstract])) AND ((((((skin cancer[Title/Abstract]) OR (skin neoplasm[Title/Abstract])) OR ("nonmelanoma"[Title/Abstract])) OR ("basal cell carcinoma"[Title/Abstract])) OR ("squamous cell carcinoma"[Title/Abstract])) OR (squamous cell cancer[Title/Abstract]))	209
Embase	(('kidney transplantation'/exp OR 'kidney transplantation') OR ('kidney transplant recipient')) AND (('prognostic factor') OR ('prognosis') OR ('immunosuppressive agent')) AND (('non melanoma skin cancer') OR ('basal cell carcinoma') OR ('squamous cell carcinoma'))	195

Table 2. Study characteristics

Author(Year)	Study design	Domain		Determinant	Outcome	Follow-up period
		Sample size	FST N (%)			
Bernat et al (2014)[9]	Ambidirectional cohort	289	FST≥ 3 128(45)	Age, FST, sun exposure, smoking, immunosuppressant therapy, induction therapy	NMSC	Median 72 months (12-180 months)
Gonçalves et al (2015)[10]	Retrospective cohort	165	Mixed race/black 97(58.8)	Age, gender, FST	NMSC	Average 72.7 months ± SD 12.9, median 75 (13-87)
Kaufmann et al (2016)[11]	Retrospective cohort	376	124(46)	Age, gender, FST, sun exposure, smoking behavior, immunosuppressant therapy, actinic keratoses	NMSC	Average 10.6 years (SD 7.4 years)
Zavattaro et al (2019)[12]	Retrospective cohort	518	359(67.7)	Age, FST, actinic chronic lesion, lentigo solar, seborrhoeic keratoses, cherry angioma, kidney disease, UV lamp exposure, sunburn history, sunscreen use, out of office occupation	NMSC	Median 9.2 years

FST = Fitzpatrick skin type; NMSC = nonmelanoma skin cancer; SD = standard deviation; UV = ultraviolet

Table 3. Critical review

Criteria	Validity					Clinical Importance		Applicability	
Author (year)	Representative study subjects	Adequate follow-up time	Objective outcome measurement	Blinding	Prognostic factor adjustment	Outcome	Precision	Based on population, intervention, and outcome	LoE†
Bernat et al (2014)[9]	+	+	+	N/A	+	Incidence cumulative, relative hazard	p value, CI	+	2b
Gonçalves et al (2015)[10]	+	+	+	N/A	-	Incidence	p value	+	2b
Kaufmann et al (2016)[11]	+	+	+	N/A	+	Incidence rate, incidence rate ratio	p value, CI	+	2b
Zavattaro et al (2019)[12]	+	+	+	N/A	+	Hazard ratio	p value, CI	+	2b

+ : yes or appropriate
- : none
N/A: not available
CI: confidence interval 95%
LoE: *Level of evidence*
† Based on The Oxford Centre of Evidence-Based Medicine

Table 4. Study outcome

Variable	Outcome	(95% CI)	p-value
Bernat et al (2014)			
- Total RTRs developing NMSC, n (%)	73 (25.2)	20-30%	
- Mean duration from kidney transplantation until the first NMSC, months	58.5		
- Cumulative incidence of NMSC from the time of kidney transplantation, %			
- 5 years after transplant	20.78	1.03-1.09	**0.001**
- 10 years after transplant	37.5		
- 15 years after transplant	53.08		
- Gender			
- Male	Ref.		
- Female	Relative hazard 0.98	0.27-0.92	**0.026**
- Phototype			
- I-II	Ref.		
- >=III	Relative hazard 0.50	1.25-3.71	**0.006**
- Occupational sun exposure			
- Low	Ref.		
- High	Relative hazard 2.15		
Goncalves et al (2015)			
- Total RTRs developing NMSC, n (%)	11 (6.67%)	2.87-10.47%	
- Mean duration from renal transplantation until diagnosis of NMSC, months (SD)	37.7 (19.1)		
- Total RTRs with NMSC and without NMSC by age, n (%)			
- < 40 years old	1 (9.1) and 64 (41.6)		**0.028**
- ≥ 40 years old	10 (90.9) and 90 (58.4)		
- Total RTRs with NMSC and without NMSC by race, n (%)			
- White	8 (72.7) and 60 (39.0)		**0.030**
- Mixed/black	3 (27.3) and 94 (61.0)		
- Average age at onset of NMSC and without NMSC, years (SD)	51.8 (8.9) and 40.7 (13.3)		**0.011**
Kaufmann dkk. (2016)			
- Total RTRs developing NMSC, n (%)	89 (23.67)	19.3-27.95	
- Mean duration from kidney transplantation until the first NMSC, years (SD)	12.56 (7.6)	11.8 – 13.3	
- Gender, n (%)			
- Male	233 (62)	1.11-2.73	**0.02**
- Female	143 (38)	-	-
Variable	**Outcome**	**(95% CI)**	**p-value**
- **Kaufmann dkk. (2016)**			
- Age			
- <35	IRR 1	1.33-4.81	**0.005**
- 35-49	IRR 2.53	2.49-8.88	**<0.001**
- 50+	IRR 4.70		
- Skin type		1.13-2.94	**0.01**
- I-II	IRR 1.82	-	-
- III-VI	IRR 1		
- Number of AK Lesions		-	-
- 0	IRR 1	1.34-3.94	**0.002**
- 1-10	IRR 2.30	2.55-6.96	**<0.001**
- >10	IRR 4.20		
- Drugs			
Ciclosporin / Tacrolimus		-	-
- No	IRR 1	1.13-7.01	**0.03**
- Yes	IRR 2.81		
Zavattaro et al (2019)			
- Total RTRs developing NMSC, n (%)	148 (28.57)	**24.67 - 32.47%**	
- Mean duration from kidney transplantation until the first NMSC, years (SD)	9.0 (7.7)		
- Gender			
- Male vs Female	HR 2.18	1.49-3.20	<0.0001
- Age at transplantation (years)			
- ≥50 vs <50 years	HR 1.08	1.06-1.10	<0.0001
- Skin type			
- I-II vs III-VI	HR 306.40	42.84-2191.32	<0.0001
- Chronic actinic damage			
- Yes vs No	HR 2.18	1.57-3.03	<0.0001
- Solar lentigo			
- Yes vs No	HR 1.46	1.03-2.08	0.03
- Previous sunburns (yes vs no)	HR 1.57	1.13-2.20	0.01

CO = confidence interval; RTR = renal transplant recipients; NMSC = nonmelanoma skin cancer; SD = standard deviation; IRR = incidence rate ratio; AK = actinic keratosis; HR = hazard ratio

DISCUSSION

Almost half of the malignancies in RTRs were NMSC, and most of them were found in RTRs with lighter skin color (FST<3).[13] Up until now, Western countries issued most of the recommendations related to NMSC in RTRs, whereas perhaps due to the low prevalence of NMSC in Asia, protocols and recommendations for complete skin examination in Asian RTRs, especially in Indonesia, are still lacking.

In countries with FST ≥3 such as in India, and South Korea, NMSC proportion in organ transplantation recipients (OTRs) were 3.12% and 3.8% respectively.[7,8] A study in Singapore, which had a majority of people with FST ≥3, stated that a prevalence of NMSC in RTRs was 4.7%. Although it seemed low in number, it was relatively high compared to the Singapore national average of NMSC cases in the normal population.[6] Another study of darker skin OTRs (Afro-American, Hispanic, and Asia) in Pennsylvania found a skin cancer incidence as high as 5.8%.[14] This further emphasizes that skin color is not the single most crucial factor for NMSC development in RTRs.

This is supported by the result of four studies, including Bernat-García et al[9], Gonçalves et al (2015)[10], Kaufmann et al (2016)[11], Zavattaro et al (2019)[12], all of which reported a relatively high NMSC prevalence in RTRs, ranging from 6 to 28.6%. The highest incidence of NMSC was found in the study by Zavattaro et al, whose subjects with FST≥3 being the most in number among other studies.[12] Based on the existing literatures, the most frequent type of NMSC in RTRs were SCC and BCC, with more SCC cases than BCC in OTRs.[15] However, Bernat-García et al and Zavattaro et al reported a reversed ratio, agreeing with what was reported in the general population.[9,12] Similar results were reported by Mackintosh et al, that is, a proportion of SCC lower than BCC by 0.4 : 1.[16] The difference in ratio between these two types of NMSC might be caused by disparities in the studies' follow-up, the existence of a second skin cancer, geographical location based on altitude and latitude, as well as the degree of sun exposure.

Darker skin color has a higher amount of melanin, which is thought to be photoprotective compared to lighter skin color. Both studies from Kaufmann et al and Zavattaro et al reported that people with FST<3 had higher risk of developing NMSC.[11,12] Although Gonçalves et al did not show the magnitude of the risk, they reported a significantly higher proportion of NMSC in white-skinned populations.[10] This was further supported by Bernat-García et al who stated that people with FST ≥3 had a protection factor against NMSC.[9]

It is generally known that NMSC occurs mainly due to UV radiation exposure. UV radiation is thought to act as a potent carcinogen which may cause DNA mutation, suppress tumor inhibitory mechanism, and induce chronic inflammation.[17] This was supported by Bernat-García et al who stated that occupational sun exposure would increase the risk of developing NMSC by 2.5 times.[9] In contrast, Zavattaro et al found no significant risk related to UV exposure.[12] Perhaps this was because more subjects reported being exposed to the sun only once in a while compared to those who reported frequent sun exposure. However, Zavattaro et al observed a significant influence of history of sunburn, solar lentigo, and chronic actinic damage on the development of NMSC in RTRs.[12] Kaufmann et al reported that an increased number of actinic keratosis lesion would increase the risk of developing NMSC in RTRs.[11] These four skin disorders are known to be closely related to UV exposure. Therefore, UV exposure and its related skin disorders correspond with the risk of NMSC in RTRs.

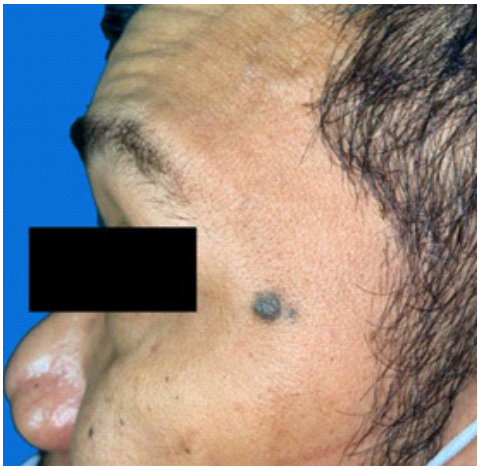

Figure 2. Skin lesion of the patient.

Another risk factor reported in all of the studies was age. Older RTRs were considered to have more risk in developing NMSC. Bernat-García et al and Zavattaro et al set their subject limits to >50 year-olds, while Gonçalves et al >40-year-olds. Although Kaufmann et al did not mention a definite cut-off for age, they stated an older age group.

Only two out of four studies examined the risk of immunosuppressant therapy in case of NMSC.[9,11] Only Kaufmann et al showed a significant result of cyclosporine or tacrolimus therapy in increasing the risk of NMSC by three times compared to other drugs.[11] Supporting theory stated the role of cyclosporine in inhibiting apoptotic keratinocyte due to UV exposure. Cyclosporine also accelerated tumor growth by increasing growth factor production and hampering mitochondrial permeability transition pores (MPTPs) opening, where MPTPs should be open during oxidative stress due to UV exposure; thus, causing gene damage.[18] Recent immunosuppressants, which are considered better than cycloscporin and tacrolimus, are inhibitors of mammalian target of rapamycin (mTOR), sirolimus, and everolimus.[19] A meta-analysis in 2014 showed the protection effect of sirolimus against NMSC was as large as 68% (adjusted hazard ratio 0.32, 0.24 to 0.42; P<0.001), but found no relation between the use of sirolimus as induction therapy (adjusted hazard ratio 0.65, 0.36 to 1.17; p=0.15).[20] Nevertheless, Bernat-García et al and Kaufmann et al failed to prove a similar relationship between the immunosuppressant agent in favor of NMSC development. In Cipto Mangungkusumo Hospital, cyclosporine is still used as the first line regiment in maintenance therapy for RTRs.

Only Bernat-García et al and Kaufmann et al did a survival analysis by showing a Kaplan-Meier curve. Both studies observed similar cumulative incidence.[9,11] These comparable results might be due to similar number of studies' population with FST < 3 (45% and 46%). In comparison with a study in Australia with an incidence of 52.2%, the number of NMSC reported by Bernat-García et al was 25.2% with a median follow up time was 6 years, and Kaufmann et al was 23.67%, with a mean of 12.56 SD 7.6 years. [9,11,21] These findings are in contrast to a study in Korea that showed lower incidence of skin cancer (1.66%) after 10 years post solid organ transplantation.[21] The results indicate the duration of immunosuppressants consumption is in line with the incidence of NMSC.

The main limitation of this study is that the included studies do not exclusively recruit people with FST ≥3 as their sample. However, since RTR with FST >3 accounts for the majority of the studies' samples, the reported outcome are still deemed to be valid with this study. This shows that research on skin cancer in RTRs of higher Fitzpatrick skin type is still in its infancy. We hope this paper could be the basis to further study the development of NMSC in RTRs with skin type ≥3, especially in Indonesia.

CONCLUSION

Better understanding about the risk factors of NMSC in RTRs could increase awareness to perform proper skin examination before and after kidney transplantation. Although RTRs with FST ≥ 3 have a lower risk of developing the cancer, other factors, aside from FST, also contribute to the occurrences of NMSC. These factors include older age, more sun exposure, history of sunburn, existing chronic actinic lesion, solar lentigo, precancerous lesion such as actinic keratoses, and prolonged cyclosporine or prolonged cyclosporine tacrolimus consumption, as was the case in this report, during maintenance therapy. This calls for preventive measures against NMSC, especially in RTRs, such as protection from sun exposure (applying sunblock before any outdoor activities or minimizing going under the sun altogether if possible) and self-skin examination (SAKURI) for precancerous and cancerous lesion.

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