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MALAYSIAN JOURNAL OF DERMATOLOGY

ORIGINAL ARTICLE

ACKNOWLEDGEMENT

Dermatological Society of Malaysia
Medical Academics of Malaysia, Unit 1.6, Level 1, Enterprise 3B, Technology Park Malaysia, Jalan Innovasi 1, Lebuhraya Puchong- Sg Besi, Bukit Jalil, 57000 Kuala Lumpur, Malaysia

MALAYSIAN J OF DERMATOLOGY
ISSN 1511-5356

Published by Dermatological Society of Malaysia twice a year from year 2009 (June and December issues)

Printed by Vanda Dynamic Enterprise
723E, 1st Floor, Vanda Business Park, Jalan Sungai Dua, 11700 Penang
Tel : 04-6584515 / 04-6578515 Fax : 04-6584505

ORIGINAL ARTICLE

Quality of Life and Its Risk Factors Among Patients with Chronic Spontaneous Urticaria In A Tertiary Center

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Abstract

Background

Chronic urticaria is a spontaneous or idiopathic mast cell driven disease which affects patients' well-being and quality of life. This study aimed to determine the prevalence of chronic spontaneous urticaria (CSU) in a public tertiary hospital, to determine patients' quality of life (QoL) and factors associated with impaired QoL.

Methods

A cross-sectional study was conducted at Dermatology Clinic, Hospital Putrajaya. Patients aged more than 18 years diagnosed with CSU were included. Patients with other chronic diseases that may affect QoL were excluded. Data was collected by face to face interview. QoL was assessed using Dermatology Quality of Life (DLQI) questionnaire. Urticaria severity was determined using Urticaria Activity Score (UAS-7).

Results

A total of 88 patients aged 40±13.9 years participated with a male to female ratio of 1:3.4. Prevalence of CSU was 0.9%. Mean total DLQI score was 6.3±5.46, 27.3% of patients had no QOL effects, 18.2% had small effect, 36.4% moderate effect and 17% very large effect. Symptoms & feelings subdomain revealed the most severe impairment, followed by leisure and daily activities. Median UAS-7 was 6, 51.1 % of patients had well-controlled disease. Higher disease activity was associated with a higher DLQI (*p=0.02*). Risk factors assessed did not show statistically significant effect on QoL.

Conclusion

CSU had moderate effect on the QoL of most patients. Symptoms and feelings, leisure and daily activities were predominantly affected. Disease activity was negatively associated with QoL impairment.

Key words: *CSU; quality of life; DLQI; UAS-7; prevalence*

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Introduction

Urticaria is a skin condition defined by wheals associated with pruritus. [1] Chronic urticaria is a clinical diagnosis when the symptoms persist daily or almost daily for longer than 6 weeks.[2] The lifetime prevalence of urticaria is about 20% whereas the point prevalence of chronic urticaria is estimated to be 1 %.[1-2] There is a female predominance, all age groups are affected

with an incidence peak around the 3rd and 4th decades. The subtypes of chronic urticaria can be divided into inducible if there is an identified provoking factor or spontaneous if no inciting factor is found. Inducible chronic urticaria can be secondary to friction, vibration, pressure, temperature, solar radiation or sweating.[3]

However, majority of cases of chronic urticaria are idiopathic or spontaneous comprising of 80% to 90% of chronic urticaria.[1] In these cases, no triggering factors are found.[1] Urticaria may or may not be associated with angioedema which causes swelling of the face, mouth, lips, upper airways, genitalia or extremities.[3] Angioedema occurs in 40% of chronic spontaneous urticaria (CSU).[4] Chronic urticaria might be associated with other autoimmune processes or chronic inflammation such as rheumatoid arthritis, systemic lupus erythematosus, ankylosing spondylitis, psoriasis, thyroid disorders and inflammatory diseases. [5]

Chronic urticaria carries a substantial health burden to affected patients and is an economic burden on society in terms of absence from work and production lost.[2,6] Quality of life (QoL) is markedly affected by chronic urticaria.[7-9] Their QoL is comparable to that of patients with atopic dermatitis, psoriasis, coronary artery disease and severe asthma.[10] Chronic urticaria affects daily life due to its unpredictable waxing and waning course, disruptive symptom of itch and difficulty in management of the condition. Urticaria affects both subjective well-being and objective functioning causing negative mood changes, sleep deprivation, poorer social relationships and general lack of energy.[10] About 60% of chronic urticaria patients had a psychiatric diagnosis.[11] There is high prevalence of depression, hysteria, hypochondria and post traumatic stress disorder.[5] Recurrent pain syndromes such as tension headaches and fibromyalgia have been described.[5] Male gender, younger age and disease severity are a few factors which have been identified to be associated with impaired QoL.[7,9] Risk for chronic spontaneous urticaria is higher in obesity, anxiety, dissociative and somatoform disorders, malignancies, use of immunosuppressive drugs and chronic use of systemic steroids. Smoking was instead associated with a significantly reduced risk of chronic spontaneous urticaria.[12]

In this study, we aimed to investigate the impact of chronic urticaria on patients' QoL and determine factors associated with impaired QoL.

Materials and Methods

This study was a cross sectional study involving patients with CSU conducted between October 2021 and May 2022 at the Department of Dermatology of Hospital Putrajaya, Putrajaya, Malaysia. Clinically diagnosed cases of CSU fulfilling the inclusion and exclusion criteria were enrolled. Written informed consent was procured.

Inclusion criteria were patients with clinical diagnosis of CSU confirmed by a dermatologist and who have been under follow up for at least 6 months, aged more than 18 years old and able to read and understand English or Bahasa Melayu.

Exclusion criteria were CSU patients with other chronic diseases that could impact QoL as follows i) malignancies, ii) diabetes mellitus with multiple end organ damage, iii) congestive cardiac failure NYHA Class III or IV, iv) chronic infectious diseases, v) immunodeficiencies, vi) chronic liver disease, vii) chronic kidney disease on renal replacement therapy as well as any other conditions that the investigator deemed inappropriate for participation. Patients with angioedema alone or chronic inducible urticaria and chronic urticaria secondary to any other diagnosis were also excluded.

Demographic data and information on clinical characteristics were collected by interviewing the patients face to face. These included age, gender, marital status, level of education, employment status, smoking history, comorbidities including atopic diseases, medications and history of allergies. Age at onset of symptoms, date of diagnosis, date of resolution of symptoms if applicable, presence of angioedema, location of angioedema, history of inducible urticaria

by physical stimuli, presence of itch, visits to Emergency department, dietary restrictions and CSU treatments were recorded. Patients were deemed to be compliant if they did not miss a single dose of medication since the last clinic appointment.

Patients were asked to complete the Dermatology Life Quality Index (DLQI) questionnaire in English or Bahasa Melayu. The DLQI comprise of 10 questions that cover patients' perception of the impact of skin diseases on different aspects of their health related quality of life over the last week. It has over 110 validated translations including in English, Bahasa Melayu and Chinese languages. The meaning of the scores are as follows; score of 0-1: no effect on patient's life, score 2-5: small effect, score of 6-10: moderate effect, score of 11-20: very large effect and score of 21-30: extremely large effect.[13] Lennox R. et al validated DLQI as an outcome measure for urticaria related quality of life in 2004.[14]

Urticaria disease activity was assessed using Urticaria Activity Score (UAS-7), a composite disease activity score with pruritus intensity score(0-21) and number of hives score (0-21) over 7 days. Prespecified cut-offs of the UAS-7 are used to divide patients by disease severity 1-6: well-controlled; 7-15: mild, 16-27: moderate, and 28-42: severe urticaria. [15]

Data was analysed using Statistical Package for Social Sciences (SPSS) version 20.0. Descriptive analysis including mean and standard deviation were used for normally distributed data whereas median and interquartile range was used when data was not normally distributed. Pearson's chi-square test, independent t-test, Mann-Whitney test and Fisher's exact test was used to determine selected risk factors that affect QoL. Spearman correlation determine relationship between UAS-7, itch and wheal with DLQI. A p-value of < 0.05 was considered statistically significant. Sample size estimation was calculated using the population mean formula. 16 Prior data indicate that the mean urticaria activity score was 1.04 (standard deviation =1.61) and population size is 80. Assuming the type 1 error probability and precision were 0.05 each, 79 samples were required to be studied. With an additional 5% drop out rate, the sample size calculated was 84 samples.

Results

The prevalence of CSU in Hospital Putrajaya during the study period was 0.9%. The demographic and clinical characteristics of the 88 study participants are tabulated in **Table 1.** There was a female predominance (3.4:1 female to male ratio) and involvement of working-age adults**.** Majority (73.9%) were employed, 20.5% unemployed or retired whereas 5.2% were students. The education level of CSU patients was distributed as followings; primary and secondary levels (28.4%), diploma and degree (67%), masters and doctorate in 4.5%. The ethnic distribution was reflective of Putrajaya population that comprises mainly government servants as Putrajaya is the administrative city of Malaysia with majority Malays (81.8%) followed by Indians (11.4%) and Chinese (4.5%). Majority were non-smokers (83%), with positive personal history of atopy (60.2%) and were married (62.5%). The mean BMI was in the overweight category (26±5.0kg/m^2) and metabolic diseases were prevalent with 14.8% having diabetes mellitus and dyslipidaemia each and 18.2% having hypertension. The median duration of CSU in the study population was 18 months with a 4 months median duration interval before diagnosis. Angioedema was present in nearly half of patients (45.5%) with 9.1% involving airways. Concomitant CIndU was reported in 30.7%.

All patients were on treatment for CSU as shown in **Table 2**. The most commonly used therapy was non-sedating H_1-antihistamine at approved doses which was used by 43(48.9%) of patients. The antihistamines include loratadine, cetirizine and bilastine. Forty three (49%) patients were on second-line up-dosed non-sedating H1-antihistamines with concurrent leukotriene antagonist in 3 patients (3.4%) and omalizumab in 4 patients (4.5%). One patient received chlorpheniramine on an as required basis which was due to good control of disease with sporadic

rare nocturnal reoccurrence of wheals impairing sleep. The vast majority were compliant to treatment (79.5%) with 13 (14.8%) reporting side effects to treatment. Main side effect was drowsiness reported by 7 (53.8%) patients. However, most patients 46(52.3%) subjectively felt their treatment was successful.

Table 1. Demographics and clinical characteristics of the study population

Characteristics	n=88 Mean±SD or n (%)
Age, years	40±13.9
Gender	
Male	20 (22.7)
Female	68 (77.3)
Ethnicity	
Malay	71 (81.8)
Chinese	10 (11.4)
Indian	4 (4.5)
Others	2 (2.3)
Marital status	
Married	55 (62.5)
Single	32 (36.4)
Widowed	1 (1.1)
Education level	
Primary/Secondary	25 (28.4)
Diploma/Degree	59(67.0)
Masters/Doctorate	4 (4.5)
Employment status	
Employed	65 (73.9)
Unemployed/Retired	18 (20.5)
Student	5 (5.7)
Smoking status	
Non-smoker	73 (83.0)
Smoker	11 (12.5)
Ex-smoker	4 (4.5)
Co-morbidities	
Others	21 (23.9)
Hypertension	16 (18.2)
Diabetes mellitus	13 (14.8)
Dyslipidaemia	13 (14.8)
Thyroid disorders	3 (3.4)
Cancer	3 (3.4)
History of atopy	53 (60.2)
BMI (kg/m^2)	26±5.0
Total duration of wheals before diagnosis (months)	4 (6.0)*
Age of onset (years)	37±14.2
Total duration of wheals (months)	18 (28.0) *
Angioedema:	40 (45.5)
Non Airway	32 (36.4)
Airway	8 (9.1)
Inducible urticaria/Concomitant CIndU	27 (30.7)

**Median (Interquartile range)*

Dietary restrictions were practised by 35(39.8%) patients with most avoiding seafood (62.9%). A low histamine diet was maintained by only 4 (4.5%) patients.

Table 2. CSU treatment

Treatment given	n=88 Mean±SD or n (%)
Loratadine: Total patients	46 (52.3)
Loratadine: Approved dose(≤10mg daily)	24 (27.3)
Loratadine: Up-dosed(>10mg daily)	22 (25.0)
Cetirizine: Total patients	32 (36.4)
Cetirizine: Approved dose(≤10mg daily)	18 (20.5)
Cetirizine: Up-dosed (>10mg daily)	14 (15.9)
Levocetirizine: Total	7 (8.0)
Levocetirizine: 5mg BD	1 (1.1)
Levocetirizine: 10mg BD	6 (6.8)
Montelukast	3 (3.4)
Omalizumab	4 (4.5)
Bilastine-Total	2 (2.3)
Bilastine : 10mg OD	1 (1.1)
Bilastine : 20mg BD	1 (1.1)
Chlorpheniramine PRN	1 (1.1)
Compliant to treatment	70 (79.5)
Subjective successful treatment	46 (52.3)
Side effects to treatment	13 (14.8)
Types of side effects: (n = 13)	
Headache	1 (7.7)
Drowsiness	7 (53.8)
Others	5 (38.5)
Practice dietary restriction(Total)	35 (39.8)
Types of dietary restriction:	
Avoid seafood	22 (25.0)
Avoid meat	6 (6.8)
Avoid nuts	6 (6.8)
Low histamine diet	4 (4.5)
Other diets	9 (10.2)

mg=milligram; BD=twice daily; OD=once daily; PRN= 'pro re nata'- as needed

Table 3. Disease severity and quality of life

Measure	n=88 Mean±SD or n (%)
Disease severity (UAS-7)	
Total UAS-7 score	6 (6.0)*
1-6: well-controlled	45 (51.1)
7-15: mild	17 (19.3)
16-27: moderate	4 (4.5)
28-42: severe	1 (1.1)
Dermatology Life Quality Index (DLQI)	
Total DLQI	6.3±5.46
0-1: No effect	24 (27.3)
2-5: Small effect	16 (18.2)
6-10: Moderate	32 (36.4)
11-20: Very Large	15 (17.0)
21-30: Extremely large	1 (1.1)

**Median (Interquartile range); UAS-7:Urticaria Activity Score*

The median UAS-7 score in patients with CSU was 6 with majority (45 patients, 51.1%) having well controlled disease. Mild disease was noted in 17(19.3%) patients, moderate disease in 4(4.5%) patients and severe disease in 1(1.1%) patient. (Table 3)

Figure 1. The effect of chronic urticaria on quality of life

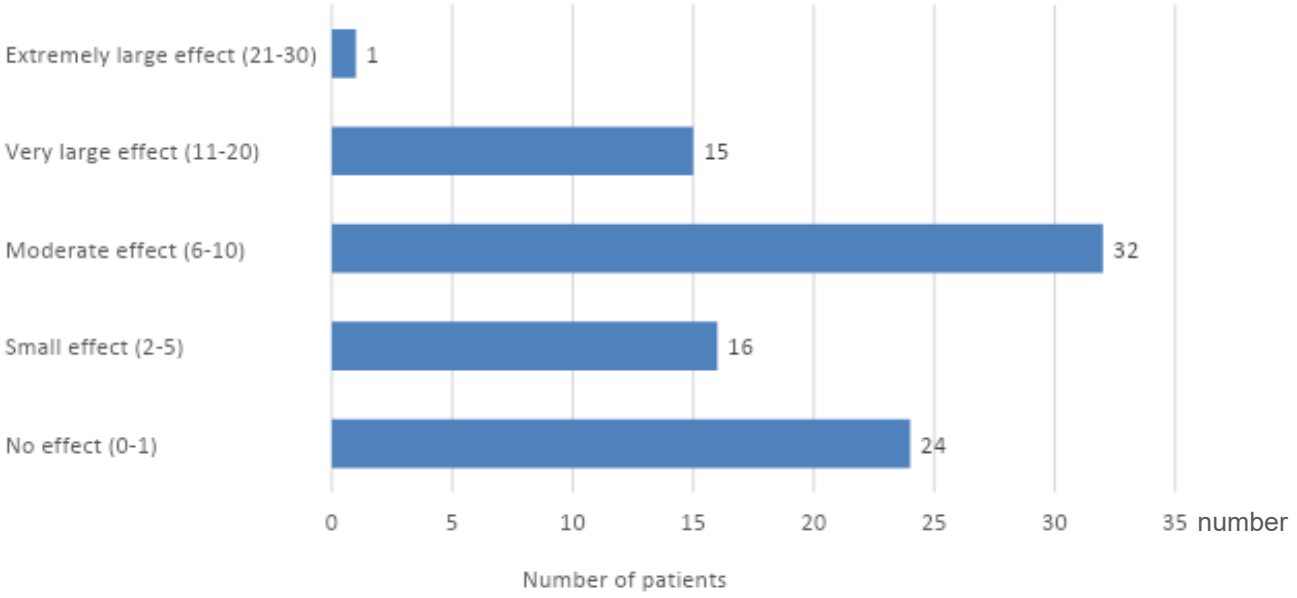

Table 4. Responses for Dermatology Life Quality Index in patients with chronic spontaneous urticaria

Category	Questions	(n)=88 Number of responses (%)				
		Very much	A lot	A little	Not at all	Not relevant
Symptoms & feelings	Over the last week, how itchy, sore, painful, or stinging has your skin been?	4 (4.5)	20 (22.7)	29 (33.0)	35 (39.8)	
	Over the last week, how embarrassed or self-conscious have you been because of your skin?	2 (2.3)	17 (19.3)	36 (40.9)	33 (37.5)	
Daily activities	Over the last week, how much has your skin interfered with you going shopping or looking after your home or garden?	2 (2.3)	9 (10.2)	37 (42.0)	40 (45.5)	
	Over the last week, how much has your skin influenced the clothes you wear?	2 (2.3)	14 (15.9)	31 (35.2)	41 (46.6)	
Leisure	Over the last week, how much has your skin affected any social or leisure activities?	4 (4.5)	9 (10.2)	31 (35.2)	44 (50.0)	
	Over the last week, how much has your skin made it difficult for you to do any sport?	2 (2.3)	10 (11.4)	35 (39.8)	32 (36.4)	9 (10.2)
Work and school	Over the last week, has your skin prevented you from working or studying?	1 (1.1)			87 (98.9)	
	If "No", over the last week how much has your skin been a problem at work or studying?		4 (4.5)	40 (45.5)	43 (48.9)	
Personal relationship	Over the last week, how much has your skin created problems with your partner or any of your close friends or relatives?	2 (2.3)		19 (21.6)	67 (76.1)	
	Over the last week, how much has your skin caused sexual difficulties?	1 (1.1)	2 (2.3)	21 (23.9)	50 (56.8)	14 (15.9)
Treatment	Over the last week, how much of a problem has the treatment for your skin been, for example by making your home messy or by taking up time?		12 (13.6)	18 (20.5)	58 (65.9)	

The overall mean DLQI score was 6.3±5.46 with most having moderate impact on quality of life. No effect in QOL was observed in 24(27.3%) patients followed by small effect in QOL in 16 (18.2%), very large effect in QOL in 15(17%) and extremely large effect on QOL in 1(1.1%) patient. (Figure 1). Both the UAS-7 and DLQI demonstrated high internal consistency (Cronbach alpha 0.83, 0.77 respectively).

Among the six subdomains of life quality measured by the DLQI questionnaire, greatest impairment was seen in symptoms and feelings as well as leisure activities with 3.4% and 3.6% participants affected very much respectively. Furthermore, 21% and 11.4% patients were affected a lot. Next mostly affected subdomain was daily activities, it was very much affected in 2.3%, a lot in 13.1% and a little in 38.6%. On the other hand, work and school subdomain was affected very much in 1.9%, a lot in 1.2% and a little in 24.7%. Treatment and personal relationship subdomains were least affected. No one was very much affected in the treatment subdomain, 13.6% were a lot affected and 20.5% were a little affected. In comparison, for the personal relationship subdomain, 1.9% were very much affected, 1.2% were a lot affected, and 24.7% a little affected. Highest prevalence of not relevant answer was on CSU activity effects on sexual relationships followed by sports activities (15.9% and 10.2% respectively) (Table 4 and Figure 2).

The mean DLQI score was not significantly different in regard to age, gender, education level, smoking status, associated angioedema and dietary restriction in CSU patients ($p>0.05$) as shown in Table 5.

Figure 2. Quality of life impairment in chronic spontaneous urticaria patients based on categories of Dermatology Life Quality Index

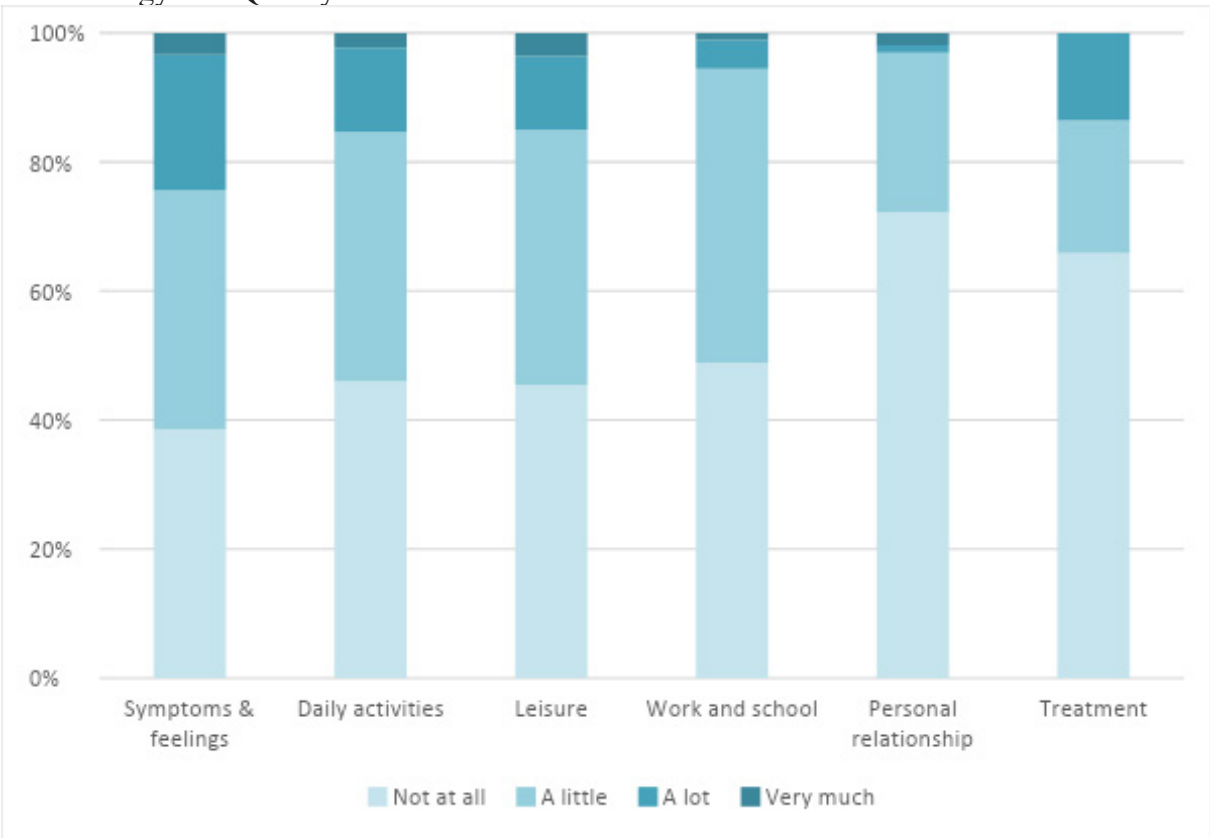

Table 5. Factors affecting quality of life

Risk factor	Small to moderate effect, DLQI score 1-10 (n)=88 mean±SD or n(%)	Very large to extremely large effect, DLQI score 11-30 (n)=88 mean±SD or n(%)	*p* value
Age			
18-40	31 (77.5)	9 (22.5)	0.14[f]
41-60	11 (61.1)	7 (38.9)	
>60	6 (100.0)	0 (0.0)	
Sex			
Male	11 (84.6)	2 (15.4)	0.37[x]
Female	37 (72.5)	14 (27.5)	
Education level			
Primary/Secondary	15 (88.2)	2 (11.8)	0.25[f]
Diploma/Degree	30 (69.8)	13 (30.2)	
Masters/Doctorate	3 (75.0)	1 (25.0)	
Smoking status			
Non-smoker	41 (75.9)	13 (24.1)	0.67[f]
Smoker	6 (75.0)	2 (25.0)	
Ex-smoker	1 (50.0)	1 (50.0)	
Associated angioedema			
Yes	23 (74.2)	8 (25.8)	0.89[x]
No	25 (75.8)	8 (24.2)	
Dietary restriction			0.14[x]
Yes	17 (65.4)	9 (34.6)	
No	31 (81.6)	7 (18.4)	
Disease severity (UAS-7)			
Total UAS-7 score	6 (4.0)*	7 (9.0)*	0.02[m]
1-6: well-controlled	36 (81.8)	8 (18.2)	
7-15: mild	11 (73.3)	4 (26.7)	
16-27: moderate	0 (0.0)	4 (100.0)	0.005[f]
28-42 : severe	1(100.0)	0 (0.0)	
Itch (Total itch score)	3.3±1.80	4.9±2.58	0.038[t]
Wheal (Total wheal score)	2.5 (1.0)*	3.0 (4.0)*	0.038[m]

**Median (Interquartile range); x=Pearson's chi-square test; t=independent t-test; m=Mann-Whitney test; f=Fisher's exact test*

UAS-7 scores showed high positive correlation with DLQI scores ($r_{s=}$0.710, p<0.001). There were statistically significant positive correlations between itch and wheal components of UAS-7 with DLQI (Table 6).

Table 6. Correlations between total UAS-7, itch score and wheal scores with quality of life (DLQI)

Disease severity	Spearman correlation	*p* value
UAS-7[1]	0.71	<0.01
Itch	0.69	<0.01
Wheal	0.70	<0.01

Discussion

The CSU prevalence of 0.9% in our study was slightly higher than reported in a recent meta-analysis showing a point and lifetime prevalence rates of 0.7% and 1.4% respectively.[17] There are large variations in prevalence of CSU with point prevalence of 0.1% in Sweden and 0.6% in Spain which could be a reflection of different geographical and cultural characteristics.[18-19] CSU is more common in females, women suffer from CSU nearly twice as often as men and up to four times in our cohort.[12,20-22] A plausible explanation of gender disparity could be the autoimmune nature of the disease in most CSU patients.[23] The mean age of patients with CSU ranged from 32 to 45 years representing productive working age.[7,10,17-18] The mean was lower in Nepal where it was 32.86 ± 12.83 years, similar to China where it was 32.94±0.70.[7,17] The mean age was higher in Germany and Japan, where it was 42.17 ± 9.24 years and 45.2 ± 11.3 years respectively.[10,18]

Around 30-50% of CSU patients suffer from angioedema with or without wheals. [4,24-27] Japan had a lower occurrence rate of only 20%. [28] Concomitant CIndU was reported in 30.7% in our study whereas globally there are varying rates ranging from 10%-50%.[25-26,28-30]

The vast majority of our CSU patients were non-smokers, a study in Italy suggested that smoking possibly has a protective effect on the risk of CSU.[12] However, Lapi et al found a higher risk of developing CSU in obese patients.[12] Obesity is associated with a chronic systemic low-grade inflammatory state which causes decreased immunological tolerance to antigens thus increasing the risk of allergy and immune-mediated diseases.[31-33] The mean BMI in our study was in the overweight category. The higher BMI in our study population was reflected by the higher rates of metabolic diseases. Majority of our patients had concomitant atopic conditions similar to other reports which showed asthma and allergic rhinitis especially being closely linked to CSU.[34-35]

All our patients were on treatment for CSU. Almost half of them were on second generation, non-sedating H_1-antihistamine at standard doses in accordance to first-line treatment recommendations of EAACI/GA²LEN/EDF/WAO guideline.[3] The remaining majority were on up-dosed non-sedating H1-antihistamine due to poor symptom control on first line treatment. Results from 29 randomized controlled trials evaluating the efficacy of H1-antihistamines in CSU indicate that half or even less of the patients responded with a complete control of symptoms to standard doses, requiring up-titration of dose.[36] The usage of concurrent leukotriene antagonist in 3 patients is based on first line treatment recommendation by the British Association of Dermatologists guidelines.[37] Leukotriene antagonist is not included in the EAACI/GA²LEN/EDF/WAO guidelines.[3] Omalizumab was third line therapy in 4 of our patients. All 4 patients reported well-controlled disease. A multicentre study including patients from Europe, Central and Latin America, Asia-Pacific, and the Middle East reported 29.6% patients on omalizumab which is more than 6 times higher than our cohort.[38] A few of our patients with poor symptom control despite up titration of antihistamines were not prescribed omalizumab due to the high cost of the medication unaffordable to many patients. Our patients' compliance to treatment was very good. Non-adherence was due to side effects to treatment mainly drowsiness.

The majority of our patients had well controlled disease. Good symptoms control reflected by lower UAS-7 could be a reflection of better clinical practice with regular follow ups to reassess patient progress and prompt therapeutic escalation of antihistamine dose. A recent local study reported majority of patients to have moderate to severe disease and severely impaired QoL.[39] However, some patients in this study were newly diagnosed CSU not commenced on treatment yet at time of DLQI measurement reflecting higher DLQI score. In another international study involving Canada, France, Germany, Italy, Spain, Netherlands and United Kingdom, the mean UAS-7 score was 17.3 suggesting moderate disease activity despite treatment with DLQI score of 9.1.[40] The overall mean DLQI score reflected moderate impact on QoL in our patients. Small effect on QoL was reported in the Japanese RELEASE study involving 552 CSU patients with mean total DLQI score of 4.8±5.1. [10] However, 41.3% of the patients in this study were prescribed oral corticosteroids. The mean DLQI score in our study is similar to that reported for vitiligo in another local tertiary center.[41] Disease impact on QoL was lower in another local study involving patients with atopic dermatitis, acne and psoriasis.[42] The QoL of CSU patients in this study was impaired and is comparable to other chronic skin conditions.

QoL impairment was associated with more severe CSU, we found significant correlation between total UAS-7 scores with DLQI scores as well as between itch score and wheal score components of UAS-7 with DLQI. This relationship has been documented by previous studies.[9,43-44] The greatest affected subdomains of QoL was symptoms and feelings as well as leisure activities followed by daily activities. Real world evidence from the ASSURE-CSU study reported greatest negative impact on symptoms and feelings and daily activities.[40] Symptoms and feeling was amongst the most affected subdomain in other studies as well.[7,20] Many patients find occurrence of wheals cause intense itchiness and feel self-conscious when wheals

appear. Amongst the highest prevalence of 'not relevant' answer in our study was regarding the effect of CSU on sexual relationships with personal relationship subdomain was one of the least affected. We postulate that this is because these issues are a taboo in our region.

Although several studies have shown that angioedema was significantly associated with worst DLQI scores, this was not seen in our study.[45-48] The impact of skin diseases on QOL has been associated with age where younger adults were affected more than the elderly and a higher impact was recorded in women compared to men.[21,42] However, these findings are inconsistent. Men with CSU had significantly greater DLQI scores than their female counterparts in Nepal.[7] In our study, more severe QoL impairment was noted almost twice as more in women than men, however the difference was not statistically significant. We did not find any QoL differences with regards to age, education level, smoking status, and dietary restriction. Asian cultural beliefs led to about a quarter of our study population blaming seafood, meat as well as nuts as the reason for their CSU causing them unnecessary food avoidance despite it not being helpful in reducing their symptoms. Healthcare providers should address and debunk these myths during consultation with recommendation for a low histamine diet instead to prevent unnecessary nutritional deprivation.[49] However, as there are no systematic double-blind controlled trials, the level of evidence for the benefit of dietary intervention is low.

Limitations

This study was conducted in a single tertiary care center causing homogeneity of patients restricting data generalization, mainly related to socioeconomic characteristics and severity of clinical conditions and may not represent the whole country's population. In addition, psychometric instruments may not accurately translate the magnitude of the impact imposed by any disease on an individual's life.

Conclusion

Chronic spontaneous urticaria has moderate consequences on QoL of patients. Impairment in quality of life correlates with disease activity. There was no association between QoL impairment and factors such as dietary restrictions, age, gender, education level, smoking, disease duration and angioedema.

Conflict of Interest Declaration

The authors have no conflict of interest to declare.

Acknowledgement

We would like to acknowledge Prof A.Y. Finlay and his team for granting us permission to use the Dermatology Life Quality Index (DLQI). We thank the Director General of Health Malaysia for his permission to publish this article.

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ORIGINAL ARTICLE

The Impact of An Education Intervention on Knowledge and Attitude Towards Scabies Among Medical Doctors in Sabah, Malaysia

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Abstract

Background

Scabies is recognised as one of the neglected tropical diseases by World Health Organisation (WHO). This study aimed to assess the knowledge and attitude towards scabies and the impact of video lecture education intervention among doctors in Sabah, Malaysia.

Methods

A cohort study was carried out among doctors working in public primary care clinics, internal medicine, emergency and paediatric departments of district and tertiary hospitals. A questionnaire on aetiology, clinical features, and management of scabies with content validation was developed. Participants were required to fill in an online self-administered pre-lecture questionnaire, watch a 10-minute video lecture and answer the post lecture questionnaire.

Results

A total of 227 participants were included. There were 55 (24.2%) participants with good knowledge score and 102 (44.9%) with good attitude score. Recent review of information about scabies (OR=2.81, 95% CI=1.24-6.34, *p=0.01*) and longer years of experience (OR=2.13, 95% CI=1.13-4.01, *p=0.02*) were significantly associated with good knowledge. Older age group was significantly associated with good attitude (OR=2.76, 95% CI=1.31-5.83, *p=0.01*). The mean knowledge score improved from 11.96±2.42 to 16.14±1.80, *p<0.01* and mean attitude score improved from 8.98±2.32 to 6.97±2.28, *p<0.01* after video lecture intervention.

Conclusion

The overall knowledge and attitude towards scabies among doctors in Sabah were inadequate. Knowledge and attitude improved significantly after a video lecture intervention.

Key words: *Scabies, neglected tropical diseases, ectoparasite*

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Introduction

Human scabies is a parasitic infestation caused by *Sarcoptes scabies var hominis*. Transmission is via skin-to-skin contact with burrowing of the fertilised female mite into the skin of an uninfected person. The microscopic mite burrows into the skin and lays eggs, eventually triggers a host immune response that leads to intense itching and rash.[1] The incubation period is 2 to

6 weeks for those without previous exposure to scabies. Individuals who have been previously infected with scabies develop symptoms within 1 to 5 days of re-exposure.[2] Classic scabies is characterised by erythematous papular eruption, serpiginous burrows, and intense pruritus. The common sites of involvement are the web spaces of fingers, wrists, extensor of elbows and knees, waist, navel, abdomen, buttocks, groins, and genitals. Crusted scabies may develop in patients who are immunosuppressed, have chronic disease such as diabetes with cutaneous sensory dysfunction of the skin.[3] Scabies is often diagnosed clinically based on history and through physical examination.[4,5] Scabies infestation may be complicated by bacterial infection, which is commonly due to *Staphylococcus aureus* and *Streptococcus pyogenes*.[4,6]

An estimated 200 million people worldwide suffer from scabies at any time.[1,4] Scabies is one of the most common dermatological condition, accounting for a substantial proportion of the skin diseases in developing countries. It is endemic in resource-poor tropical settings, among infants, children, and adolescent. The estimated average prevalence in children is 5-10%.[1] The highest rates of infestation occur in countries with hot, tropical climates, especially in communities where overcrowding and poverty co-exist, and where there is limited access to treatment.[7,8] The number of inpatient management for scabies in a developed country was reported to increase from 960 in 2012 to 10,072 in 2019.[3]

In Malaysia, the prevalence of scabies was 11.6% in the palm oil and rubber estate settlements, with the worst affected being those in the 5-9 years old age group (24%).[9] The prevalence of scabies was 31% among children living at a welfare home.[10] On the other hand, 8.1% of the students staying in the secondary boarding schools had scabies.[11] Misdiagnosis and suboptimal management can result in community or nosocomial outbreak, rendering it more challenging to treat.[5]

The primary objective of this study was to evaluate the knowledge and attitude of medical doctors on scabies diagnosis and management. Our secondary objectives were to evaluate the factors associated with good knowledge, compare the knowledge between the medical doctors in primary care and hospitals, and to determine post lecture knowledge and attitude after a video-based education intervention.

Materials and Methods

Study Design

This was a cohort study carried out among medical doctors working in the public primary care clinics, internal medicine, emergency and paediatric departments of district and tertiary hospitals in Sabah, Malaysia between October 2021 and May 2022. This study received ethical approval from the Malaysian Research and Ethics Committee (NMRR-21-1339-60594).

Sample size estimation was calculated using the population proportion formula (Lenneshow, Hosme, Klar, Lwanga & Organization 1990). Based on a study conducted in Saudi Arabia, the prevalence of satisfactory knowledge (≥75%) was 17.1%.12 If type 1 error probability and precision are 0.05 and 0.05, 218 subjects would be required.

The targeted medical doctors were recruited using convenience sampling. An invitation email was sent to all primary care clinics, district, and tertiary hospitals in Sabah. Google form was utilised for the consent, pre- and post- lecture questionnaires and dissemination of the video lecture link. The inclusion criteria were the medical doctors working in primary care clinics, internal medicine, emergency and paediatric departments of district and tertiary hospitals with clinical experience of at least 6 months. The exclusion criteria were house officers. Participants were required to fill in an online self-administered pre-lecture questionnaire, watch a video lecture followed by completion of the post-lecture questionnaire.

Questionnaire development

A self-administered questionnaire was generated. The content validity of the questionnaire was evaluated by 5 consultant dermatologists. The

dermatologists rated each question on a four-point Likert scale (1 indicates a totally irrelevant content; 2 indicates irrelevant content; 3 indicates relevant content; 4 indicates extremely relevant content). Subsequently a content validity index (CVI) was derived for each item, which was the proportion of reviewers who rated the item 3 or 4. Only questions with CVI 1 were included in the final questionnaire.

Data on demographic characteristics were collected. Knowledge component included the pathogen, incubation period, transmission, age susceptibility, clinical presentation, diagnosis, and management. All questions pertaining to knowledge were multiple-choice questions with one correct answer, except the question on "mode of transmission" that had three possible correct answers and one wrong answer. There were 2 questions with picture images. The first question tested on the ability to recognise typical presentation of scabies infestation which was a picture of hands with crusted papular lesions. The subsequent question tested on the recognition of burrow sign which is pathognomonic of scabies. One point was awarded for each correct answer (maximum score of 18). The score was then converted to a 100-point percentage scale for interpretation. The scores were categorized into good (≥75%), moderate (40-75%) and poor (<40%).

The evaluation of attitude was based on Likert scale (1 indicates totally disagree; 2 indicates disagree; 3 indicates neutral; 4 indicates agree; 5 indicated totally agree) giving a total possible maximum score of 20. Lower total score indicates better attitude. A score of ≤ 8 was regarded as good attitude and score of >8 was regarded as poor attitude.

The 10 minutes video lecture covered the introduction, transmission, age susceptibility, clinical presentation, diagnosis, pharmacologic and non-pharmacological treatment. The video lecture was prepared and delivered by the corresponding author. The link to the video lecture is available at https://youtu.be/QaMMzyNjMdI

Participants received 2 electronic mails throughout this study. The first email was the pre-lecture questionnaire, followed by a pre-recorded video lecture and post-lecture questionnaire for those who had submitted the complete pre-lecture questionnaire by email to the investigators.

Statistical Analysis

Data entry and analysis were done using IBM Statistical Package for Social Sciences statistical software version 25. Continuous variables were expressed as mean ± standard deviation if normally distributed and median ± interquartile range if not normally distributed. Categorical variables were reported as frequencies and percentages. Statistical significance was determined by a p value of <0.05.

Socio-demographic and professional characteristics were compared between medical officers with poor and good knowledge. Chi-square or Fisher's exact test, as appropriate, were used to examine differences in categorical variables. The factors associated with good knowledge were analysed using linear regression test. The difference between pre- and post-lecture knowledge and attitude score were analysed using paired T-test.

Results

A total of 227 participants were included in the final analysis. Table 1 shows the demographic and professional characteristics of the participants. The majority (89.4%) of the participants were medical officers while the rest were specialists. The participation of medical doctors from the primary care and hospitals (district and tertiary) were almost equal, which were 117 and 110 respectively. Fifty-four percent of the medical doctors had less than 5 years of working experience. Most of them had seen patients with scabies (95.0%). The last time information on scabies was reviewed within a month, a year and more than a year were 69 (30.4%), 90 (39.6%), 68 (30.0%) respectively. The most frequent source of information was from websites, followed by textbook and clinical practice guidelines (CPG). There were

55 participants (24.2%) with good knowledge score and 102 participants (44.9%) with good attitude score prior to viewing the video lecture.

Table 1. Demographic and professional characteristics of the participants

	n=227 n (%)
Age	
25-34	187 (82.4)
35-44	40 (17.6)
Designation	
Medical officer	203 (89.4)
Specialist	24 (10.6)
Specialty	
1.Hospital	110 (48.5)
a) Internal medicine	62(56.4)
b) Paediatric	18(16.4)
c) Emergency	30(27.2)
2.Primary care	117 (51.5)
Working experience, years	
<5	123 (54.2)
≥5	104 (45.8)
Ever encountered patients with scabies	
Yes	216 (95.2)
No	11 (4.8)
Number of scabies cases encountered	
<10	101 (44.5)
≥10	126 (55.5)
The last time information on scabies was reviewed	
Within a month	69 (30.4)
Within a year	90 (39.6)
More than one year	68(30.0)
Source of information	
1.Websites	179 (78.9)
2.Textbook	111 (48.9)
3.Journal	37 (16.3)
4.CPG	101 (44.5)
5.Video lecture	9 (4.0)

The participants performed best in the category of diagnosis (88.0%) followed by age susceptibility (81.6%), pathogen and incubation (61.9%), management (58.8%) and transmission (31.2%). Table 2 shows the responses to individual questions on knowledge and attitude.

Table 3 shows the univariate and multivariate logistic regression analysis of the potential predictors for good knowledge. Recent review of information about scabies (OR=2.81, 95% CI=1.24-6.34, *p=0.01*) and longer years of working experience (OR=2.13, 95% CI=1.13-4.01, *p=0.02*) were significantly associated with good knowledge. The younger age group (59.9%) had more participants with poor attitude as compared to the older age group (32.5%). Among the participants who had seen less than 10 cases of scabies, 64(63.4%) had poor attitude. Older age group was significantly associated with good attitude (OR=2.76, 95% CI 1.31-5.83, *p=0.01*).

Among the 227 participants, 200 participants completed both the pre- and post-video lecture viewing questionnaires. The mean pre-lecture score for knowledge was 11.96±2.42, $p<0.01$, while the mean post-lecture score was 16.14±1.80, $p<0.01$. The mean pre- and post-lecture attitude score were 8.98±2.32, $p<0.01$ and 6.97±2.28, $p<0.01$ respectively. There was a significant improvement in both the knowledge and attitude score after the video lecture viewing ($p<0.01$).

Discussion

In Sabah, a retrospective review of referral data from November 2021 to June 2022 showed 13.5% of paediatric dermatology consult for skin infection or infestation were for scabies.[12] Almost all of our study participants had managed patients with scabies. Among them, 24.2% had good overall knowledge, which is higher than a study conducted in Saudi Arabia that showed only 17.1% of primary care physicians had adequate knowledge.[13] Knowledge on aetiology and mode of transmission of our participants were good which is similar to a study conducted in Belgium where the participants had the highest score in mode of transmission.[14] However, most of our participants were unaware that scabies is an obligate human parasite and did not know the incubation period prior to development of symptoms. Our study cohort did well in diagnosing scabies correctly based on clinical images. Basic knowledge in management of scabies such as topical anti-scabietic agents and method of application are good as compared to a study conducted in Pakistan in which most of the general practitioners knew about topical anti-scabietic agents but lacked knowledge on the correct application.[15] In our study, most of the participants were unaware of the management of contacts, environment de-infestation and treatment of special patient populations like infants. One third answered correctly on the unlikely possibility of transmission from pets.

Table 2. Comparison of participants' responses to knowledge and attitude items at baseline and post-education intervention

Knowledge Items	Pre-education intervention n=227 n (%)	Post-education intervention n=200 n (%)
1. Which pathogen below causes scabies?		
a. Bacterial	11 (4.8)	1 (0.5)
b. Viral	1 (0.4)	1 (0.5)
c. Fungal	9 (4.0)	1 (0.5)
d. Parasitic*	206 (90.8)	197 (98.5)
2. How long is the incubation period for scabies?		
a. <24 hours	7 (3.1)	2 (1.0)
b. 1-3 days	67 (29.5)	13 (6.5)
c. 1-2 weeks	77 (33.9)	33 (16.5)
d. 4-8 weeks*	76 (33.5)	152 (76.0)
3. What is the mode of transmission for scabies? (may choose more than 1)		
a. Direct contact*	218 (96.0)	199 (99.5)
b. Sexual contact*	55 (24.2)	163 (81.5)
c. Contaminated clothes*	182 (80.1)	187 (93.5)
d. Swimming pool	12 (5.3)	0 (0.0)
4. Can human contract scabies from pets?		
a. Yes	134 (59.0)	51 (25.5)
b. No*	93 (41.0)	149 (74.5)
5. Which group of patients below is more susceptible to scabies?		
a. Infant	21 (9.3)	22 (11.0)
b. Children and young adult*	185 (81.5)	165 (82.5)
c. Adult	2 (0.9)	0 (0.0)
d. Elderly	19 (8.3)	13 (6.5)
6. Which of these patients below most likely has scabies?		
a. Patient A*	213 (93.8)	198 (99.0)
b. Patient B	0 (0.0)	0 (0.0)
c. Patient C	0 (0.0)	0 (0.0)
d. Patient D	14 (6.2)	2 (1.0)
7. Which of the images below best represents the pathognomonic sign of scabies?		
a. Image 1	10 (4.4)	1 (0.5)
b. Image 2	25 (11.0)	19 (9.5)
c. Image 3	12 (5.3)	5 (2.5)
d. Image 4*	180 (79.3)	175 (87.5)
8. What is the severity of Norwegian scabies?		
a. Mild scabies	14 (6.2)	1 (0.5)
b. Self-limited	24 (10.6)	1 (0.5)
c. Nodular scabies	50 (22.0)	11 (5.5)
d. Severe scabies*	139 (61.2)	187 (93.5)
9. Can scabies be diagnosed clinically?		
a. Yes*	226 (99.6)	198 (99.0)
b. No	1 (0.4)	2 (1.0)
10. How would you advice patient on the correct application of benzyl benzoate lotion?		
a. Rinse off after 8 to 12 hours	23 (10.1)	2 (1.0)
b. Rinse off after 24 hours	16 (7.0)	5 (2.5)
c. Rinse off after 24 hours then reapply for2-3 days (with baths taken between each application) *	108 (47.6)	175 (87.5)
d. Rinse off after 8 to 12 hours then reapply for 2-3 days (with baths taken between each application)	80 (35.3)	18 (9.0)
11. What is the treatment of choice for uncomplicated scabies in adult population?		
a. Fluconazole	3 (1.4)	0 (0.0)
b. Permethrin lotion 5%*	222 (97.8)	199 (99.5)
c. Ivermectin	1 (0.4)	0 (0.0)
d. Praziquantel	1 (0.4)	1 (0.5)
12. What is the drug of choice for treatment of scabies in children less than 2 months old?		
a. Ivermectin	4 (1.7)	1 (0.5)
b. Lindane lotion 1%	44 (19.4)	2 (1.0)
c. Permethrin lotion 5%	122 (53.7)	41 (20.5)
d. Sulfur ointment (5-10%) *	57 (25.2)	156 (78.0)
13. Do asymptomatic household contacts of a patient with scabies need to be treated?		
a. Yes*	167 (73.6)	196 (98.0)
b. No	60 (26.4)	4 (2.0)
14. Permethrin should be applied on the itchy lesions only in order to avoid toxicity.		
a. True	54 (23.8)	17- (8.5)
b. False*	173 (76.2)	183 (91.5)

15. Which of the statements below describes the proper management of infested environment?		
a. Spray or fumigate	3 (1.4)	1 (0.5)
b. Washing sheets and clothes at 30°C	43 (18.9)	18 (9.0)
c. Washing sheets and clothes at 50°C or covering items with a plastic bag for more than 2-3 days*	161 (70.9)	180 (90.0)
d. Washing sheets and cloths with soap	20 (8.8)	1 (0.5)
16. How long does it take after scabies treatment for the patient to be non-infectious?		
a. 24 hours*	42 (18.5)	169 (84.5)
b. 48-72 hours	99 (43.6)	21 (10.5)
c. One week	51 (22.5)	6 (3.0)
d. 2 weeks	35 (15.4)	4 (2.0)
Attitude Items		
1. Mrs Belle enquired regarding ways to prevent scabies infestation as she is anxiously preparing for the arrival of her new born baby. She found information from a magazine which suggested weekly change of mattresses and pillows. What is your thought?		
a. Totally disagree	18 (7.9)	38 (19.0)
b. Disagree	47 (10.7)	85 (42.5)
c. Neutral	56 (24.7)	29 (14.5)
d. Agree	88 (38.8)	38 (19.0)
e. Totally agree	18 (17.9)	10 (5.0)
2. Mr Andrew was diagnosed with scabies and prescribed with Permethrin 5%. His family is worried and requested him to be quarantined for 1 week. What is your thought?		
a. Totally disagree	27 (11.9)	101 (50.5)
b. Disagree	102 (44.9)	74 (37.0)
c. Neutral	41 (18.1)	14 (7.0)
d. Agree	48 (21.1)	11 (5.5)
e. Totally agree	9 (4.0)	0 (0.0)
3. A 5-year-old boy, Jack was diagnosed with scabies and he has a twin brother who he shares all his belongings with. His parents think it is ok for them to continue exchanging clothes, towels, and bedding while Jack is on treatment because they do not want any of them to feel left out. What is your thought?		
a. Totally disagree	158 (69.6)	146 (73.0)
b. Disagree	57 (25.1)	46 (23.0)
c. Neutral	2 (0.9)	3 (1.5)
d. Agree	9 (4.0)	5 (2.5)
e. Totally agree	1 (0.4)	0 (0.0)
4. A 10-year-old girl who was diagnosed with scabies and has completed treatment came home from school crying because her teacher had arranged a seat at the corner of the class and instructed her classmates to keep a distance from her. What do you think of the teacher's action?		
a. Totally disagree	123 (54.2)	145 (72.5)
b. Disagree	66 (29.1)	40 (20.0)
c. Neutral	10 (4.4)	8 (4.0)
d. Agree	25 (11.0)	3 (1.5)
e. Totally agree	3 (1.3)	4 (2.0)

**signifies the correct answer*

The poor overall knowledge score observed in our study population was associated with lack of clinical exposure and duration of work experience. Slightly more than half had 5 years or less work experience and 44.5% had encountered less than 10 patients with scabies. Predictors for good knowledge were longer years of working experience and more recent review of information about scabies. Information on scabies is easily accessible through reliable sources such as the Malaysia Clinical Practice Guideline and the Centers for Disease Control and Prevention. These sources provide comprehensive details regarding clinical manifestations, diagnosis, and treatment of the condition.

Similarly in Saudi Arabia, shorter time since last exposure to information on scabies and longer years of work experience were independent predictors for better knowledge.[13] In Belgium, clinical specialty (dermatologist vs general practitioner), number of years of work experience and number of scabies patients seen per year had significant effect on knowledge score.[14] However, there was no correlation between years of working experience with good knowledge among the general practitioners in Pakistan.[15]

The percentage of participants in our study with overall good attitude score was much higher than their overall knowledge score. However, still less than half (44.9%) had good overall

attitude score. The younger age group and those that had encountered less scabies patients were associated with poor attitude. Near one fifth thought a patient with scabies who had undergone treatment need to be quarantined for a week. Patients with scabies are often stigmatised and excluded from social interaction. The psychosocial consequences may impact their quality of life.[16,17] Students afflicted with scabies encountered numerous issues, including social exclusion, insults, challenges in writing and attending classes due to the nocturnal itching-induced sleep difficulties, as well as a scarcity of sufficient sleep time.[18] Attitude and knowledge were closely related among our cohort and the associated factors and predictors were parallel.

Like knowledge score, the mean attitude score improved significantly after the video lecture intervention. This was an encouraging outcome as a short 10-minute video lecture improved both the participants' knowledge and attitude. Scabies is not a complicated disease, nor it is difficult to learn. Education intervention is effective, secondary school children showed significantly higher knowledge and attitude scores following health education on personal hygiene practices.[19] A similar study design showed an increase of knowledge score in all components of scabies (aetiology, clinical symptoms, treatment, transmission, and prevention) among students in a boarding school in East Jakarta after a one-hour lecture on scabies.[20]

Primary care physicians' referral decisions for dermatological conditions were influenced by various factors, including diagnostic challenges, patient preferences, and resource availability, emphasizing the need for enhanced training and infrastructure to decrease unnecessary referrals and improve patient outcomes.[21] Limited exposure to dermatology in undergraduate curriculum also contributes to lower confidence in managing dermatological condition compared to other systemic diseases.[22] Dermatological diagnoses made by primary care physicians had an overall score of 56% in agreement with dermatologists' diagnoses. There was only moderate agreement on the diagnosis of scabies.[23] The patients with scabies were diagnosed as eczema, dermatophyte infection, urticaria and pyoderma by primary care physicians.[23]

Table 3. Predictor for good knowledge and attitude towards scabies among the study population

	Knowledge		Attitude	
	Crude OR, 95% CI	**Adjusted OR, 95% CI**	**Crude OR, 95% CI**	**Adjusted OR, 95% CI**
Age group				
25-34 years	1.00 (ref.)			
>34 years	1.23, 0.57-2.67	-	3.10, 1.50-6.39	2.76, 1.31-5.83
Designation				
Medical officer	1.00 (ref.)			
Specialist	1.33, 0.52-3.40	-	2.22, 0.93-5.31	1.68, 0.66-4.23
Years of working experience				
<5 years	1.00 (ref.)			
≥5years	1.93, 1.04-3.58	2.13, 1.13-4.01	1.36, 0.80-2.30	-
Specialty				
Primary care	1.00 (ref.)			
Hospital (Internal medicine, Pediatric, Emergency department)	0.77, 0.42-1.43	-	1.04, 0.62-1.76	-
Scabies experience				
Yes	1.00 (ref.)			
No	0.68, 0.14-3.26	-	0.26, 0.05-1.22	3.64, 0.76-17.56
Last time information about scabies has been reviewed				
More than one year	1.00 (ref.)			
Within last month	2.49, 1.12-5.52	2.81, 1.24-6.34	1.48, 0.75-2.92	-
Within last year	1.25, 0.56-2.79	1.34, 0.59-3.02	1.48, 0.78-2.80	-

Enhancing knowledge about scabies requires a multifaceted approach involving various strategies. Firstly, it is crucial to provide dermatology updates specifically tailored for medical doctors. These updates can take the form of specialized educational sessions or workshops, focusing on scabies management, where the latest treatment guidelines, and best practices can be discussed and shared. Additionally, there should be a re-evaluation of the medical curriculum to incorporate comprehensive training on scabies. By integrating scabies diagnosis, treatment, and management into the curriculum, medical students can receive foundational knowledge on the condition during their undergraduate education, ensuring they are well-prepared to handle cases in the future. Training programs should also be developed for nurses, equipping them with the necessary skills to recognise signs of scabies infection, counsel patients, and implement appropriate management strategies.

To reach a wider audience, educational resources such as video lectures should be created not only for doctors but also for other healthcare providers like nurses and medical assistants. These videos can cover various aspects of scabies, including diagnosis, treatment, prevention, and patient counselling, ensuring that a diverse range of healthcare professionals are well-informed. Beyond healthcare facilities, school visits can be organized to raise awareness about scabies among students, parents, and teachers. Interactive sessions can be conducted to educate them about scabies transmission, preventive measures, and the importance of seeking timely medical attention. By implementing these various approaches, we can effectively increase knowledge about scabies among healthcare providers, patients, and the public, ultimately leading to improved prevention, treatment, and management of the condition.

Limitations

The use of convenience sampling to recruit medical doctors may introduce selection bias and limit the generalizability of the findings. The sample may not be representative of all medical doctors in the target population, potentially impacting the external validity of the study. Reliance on self-administered questionnaires introduces the possibility of response bias.

Conclusion

Overall knowledge and attitude on scabies were inadequate among medical doctors in Sabah. Knowledge and attitude improved significantly after a short video lecture. This calls for regular educational and training efforts. All groups of doctors should be targeted and video lecture may be utilised as an effective mode of education intervention.

Conflict of Interest Declaration

The authors declare that they have no conflicts of interest related to this study.

Acknowledgement

We would like to thank the Director General of Health Malaysia of his permission to publish this article.

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ORIGINAL ARTICLE

Cutaneous Adverse Drug Reactions Among Oncology Patients on Targeted Therapy in a Tertiary Hospital

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Abstract

Background

Targeted therapies are associated with cutaneous adverse drug reactions (cADRs) which impair patient's quality of life. This study aimed to determine the prevalence, clinical pattern, risk factors and outcome of cADRs among oncology patients receiving targeted therapy in a tertiary hospital.

Methods

This was a cross-sectional, single-centre study conducted from 1st August 2021 to 31st January 2022. Patients were screened for cADRs and instructed to report any cutaneous reactions. Once confirmed, the clinical features and outcome of cADRs at 3 months were recorded.

Results

A total of 88 out of 152 patients on targeted therapy had developed cADRs, giving a prevalence rate of 57.9%. The most frequent cADRs seen were xerosis (21.7%) and paronychia (16.4%). The commonest culprit drug groups were the epidermal growth factor receptor inhibitors (56.8%) and multikinase inhibitors (33.6%). Only 3 cADRs were of severity grade >3. Sunscreen use was significantly lower among patients who develop cADRs. Cancer patients with comorbidities and Eastern Cooperative Oncology Group (ECOG) performance status ≥2 were 2.09 and 2.24 times more likely to have cADRs, compared to their respective counterparts. Most patients with cADRs reported improvement / resolution of symptoms (66.4%).

Conclusion

The prevalence of cADRs was 57.9%. Xerosis and paronychia were the commonest reactions seen. Concurrent comorbidities and worse ECOG performance status were associated with higher risk of developing cADRs. The majority of cADRs were mild and did not require treatment withdrawal. Pre-treatment counselling on cADRs may ensure compliance to targeted therapy.

Key words: *Oncology, targeted therapy, cutaneous reactions*

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Introduction

The incidence of cancer and its associated mortality is increasing worldwide, including in Malaysia.[1] Many antineoplastic agents are available for the treatment of cancers, including conventional chemotherapy, hormonal therapy, targeted therapy, and immunotherapy.

In recent years, advancements in targeted therapy for cancer, such as small molecule inhibitors, monoclonal antibodies, and immunotherapy, have dramatically improved survival for cancer patients. These treatments target specific molecules, oncogenic drivers, or checkpoint proteins to inhibit cancer progression and metastases.[2] Commonly used targeted therapy agents include epidermal growth factor inhibitors (EGFRI), multi-kinase inhibitors, cyclin-dependent kinase inhibitors, and vascular endothelial growth factor inhibitors.

However, targeted therapies are associated with specific side effects, particularly cutaneous adverse drug reactions (cADRs). These reactions significantly impair patients' quality of life, causing morbidity and emotional distress.[3–5] The incidence of rash with EGFRI is as high as 66% to 81% in Asia.[6–8] Factors such as age, gender, skin type, genetic predisposition, performance status and lifestyle have been shown to be associated with the development of cADRs.[4,9,10]

Recognizing cADRs is important as they have a great impact in the overall management of oncologic patients. Knowledge on the frequency of these reactions, as well as recognizing the risk factors, clinical pattern, and severity of cADRs will be helpful in planning effective pre-treatment counselling and early detection of cADRs during treatment thus ensuring better compliance by patients.

This study aimed to determine the prevalence, clinical pattern, risk factors and treatment outcome of cADRs among oncology patients receiving targeted therapy.

Materials and Methods

This was a cross-sectional single-centre study conducted from 1st August 2021 to 31st January 2022 among oncology patients on targeted therapy in a state hospital. This hospital is the main tertiary referral centre for oncology patients in the southern region of Malaysia.

Inclusion criteria was patients aged 18 years and above who attended the oncology clinic and are on targeted therapy such as tyrosine kinase inhibitors, EGFRI, antiangiogenetic agents, cyclin-dependent kinase 4/6 (CDK4/6) inhibitors and human epidermal growth factor receptor 2 (HER2) inhibitors. Written consent was obtained from all subjects. Sample size estimation was calculated using the population proportion formula by Lwanga et al.[11]

At first visit, demographic data, medical history, and drug history were obtained from electronic medical database. Cross-referencing was done with pharmacy database to confirm the treatment received. Patients were also screened for presence of ongoing cADRs and were instructed to immediately report any new cutaneous reactions throughout the study period. Skin care practices such as the use of sunscreen and moisturizers were also assessed. Once a cADR is reported, the diagnosis will be confirmed by a trained dermatologist. Patients who develop cADRs due to other causes such as radiotherapy-induced dermatitis, allergic contact dermatitis and chronic itching diseases, or due to intentional or accidental poisoning of medication, drug overdose or drug abuse and intoxication were excluded. Causality was assessed using the WHO-UMC causality scale and Naranjo's Assessment Scale, while preventability was assessed using the Schumock and Thornton scale.[12–14]

For all patients with confirmed cADRs, the clinical pattern was recorded and the severity was graded according to the Common Terminology Criteria for Adverse Events (CTCAE) v5 grading.[15] All cADRs were subsequently managed as per standard clinical management and the outcome (improvement, resolution, no improvement) at 3 months was recorded.

The study was conducted in compliance with ethical principles outlined in the Declaration of Helsinki and Malaysia Good Clinical Practice Guideline. Ethical approval was obtained from the Medical Research and Ethics Committee, Ministry of Health Malaysia with the research code of NMRR-21-1248-60489.

Table 1. Demographic data and clinical characteristics of patients with and without cutaneous adverse drug reactions (cADRs)

		With cADRs	Without cADRs	*p-value*
Age, mean (SD), years		59.8 (11.6)	55.2 (12.6)	0.02
Gender	Male, n(%)	39 (44.3)	27 (42.2)	0.79
	Female, n(%)	49 (55.7)	37 (57.8)	
Ethnicity	Malay, n(%)	33 (37.5)	26 (40.6)	0.76
	Chinese, n(%)	50 (56.8)	35 (54.7)	
	Indian, n(%)	3 (3.4)	3 (4.7)	
	Others, n(%)	2 (2.3)	0 (0.0)	
BMI, median (IQR)		21.7 (7.5)	23.9 (7.0)	0.087
Cancer Types	Breast cancer, n(%)	10 (11.4)	18 (27.3)	<0.01
	Colorectal cancer, n(%)	7 (8.0)	7 (10.6)	
	Lung cancer, n(%)	45 (51.1)	12 (18.2)	
	Ovarian cancer, n(%)	1 (1.1)	2 (3.0)	
	Liver cancer, n(%)	2 (2.3)	2 (3.0)	
	GIST, n(%)	7 (8.0)	15 (22.7)	
	Thyroid cancer, n(%)	2 (2.3)	2 (3.0)	
	Others, n(%)	3 (3.4)	3 (4.5)	
Treatment duration, median (IQR), weeks		32 (45)	33 (66)	0.73
Comorbidities, n(%)		49 (55.7)	24 (37.5)	0.03
	Diabetes, n(%)	14 (15.9)	12 (18.8)	0.65
	Hypertension, n(%)	41 (46.6)	19 (29.7)	0.04
	Heart Disease, n(%)	2 (2.3)	2 (3.1)	0.75
	Liver Disease, n(%)	5 (5.7)	1 (1.6)	0.40
	Dyslipidaemia, n(%)	7 (8.0)	5 (7.8)	0.97
	Renal impairment, n(%)	3 (3.4)	1 (1.6)	0.64
	Others[a], n(%)	13 (14.8)	6 (9.1)	0.32
ECOG Grade	<2,n(%)	58 (65.9)	52 (81.3)	0.04
	≥2, n(%)	30 (34.1)	12 (18.8)	
Lifestyle	Smoking (current smokers), n(%)	14 (15.9)	6 (9.4)	0.24
	Moisturiser use, n(%)	20 (22.7)	19 (29.7)	0.33
	Sunscreen use, n(%)	1 (1.1)	9 (14.7)	<0.01
Atopy history, n(%)		7 (8.0)	8 (12.5)	0.35
History of drug allergy, n(%)		8 (9.1)	8 (12.5)	0.50
Family history of drug allergy, n(%)		3 (3.4)	3 (4.7)	0.70
Cancer Stage	1, n(%)	1 (1.1)	0 (0.0)	0.07
	2, n(%)	1 (1.1)	2 (3.1)	
	3, n(%)	5 (5.7)	10 (15.6)	
	4, n(%)	81 (92.1)	52 (81.3)	
Fitzpatrick Skin Type	I, n(%)	0 (0.0)	0 (0.0)	0.66
	II, n(%)	1 (1.1)	0 (0.0)	
	III, n(%)	9 (10.2)	11 (17.2)	
	IV, n(%)	50 (56.8)	35 (54.7)	
	V, n(%)	27 (30.7)	18 (28.1)	
	VI, n(%)	1 (1.1)	0 (0.0)	
Number of drugs, median (IQR)		2 (2.0)	1 (1.0)	0.42
	< 3 drugs, n(%)	65 (73.9)	48 (75.0)	0.87
	≥ 3drugs, n(%)	23 (26.1)	16 (25.0)	

GIST=gastrointestinal stromal tumour; ECOG=Eastern Cooperative Oncology Group performance scale; SD=standard deviation; IQR=interquartile range

[a]Others include other chronic diseases such as thyroid diseases, stroke, rheumatological disorders and psychiatry disorders

Data Analysis

Data was analysed using SPSS version 25. Descriptive statistic was used for analysis of demography, clinical pattern, and treatment outcome. All values were reported as mean, standard deviation of the mean, median values with ranges or frequency and percentages. Categorical data was analysed using Chi-square or Fisher's exact test.

Binary logistic regression model was used to identify the risk factors associated with developing cADRs. Multiple logistic regression analysis was further performed to determine significant independent risk factors for cADRs. A p-value of less than 0.05 was considered statistically significant.

Results

Demographic Characteristics and Prevalence of cADRs

One hundred and fifty-two patients comprising 66 males (43.4%) and 86 females (56.6%) were recruited during the study period. This multi-ethnic cohort consist of 59 (38.8%) Malay patients, 85 (55.9%) Chinese patients, 6 (39.5%) Indian patients and 2 (13.2%) patients of other ethnicities. One hundred and thirty-one patients (86.2%) were at Stage 4 cancer when targeted therapy was commenced. The most common malignancy seen was lung cancer (n=57, 37.5%), while the most frequently prescribed targeted therapy was EGFRI (n=57,37.5%) followed by the tyrosine kinase inhibitors (n=51,33.6%).

A total of 88 out of 152 patients experienced at least 1 cutaneous adverse drug reaction, yielding a prevalence rate of 57.9%. There were 143 cADR events reported. The mean age of patients with cADRs was 59.8 years, comprising 44.3% males and 55.7% females. Most of the patients (54.5%) who developed cADRs were aged ≥60 years. The median number of drugs used, including concurrent non-cancer medications, was 2. Comparison between patients with and without cADRs showed significance difference in the type of malignancy, presence of comorbidities, hypertension, Eastern Cooperative Oncology Group (ECOG) grade and sunscreen use. There were more patients with breast cancer and GIST, and more sunscreen use among those without cADRs. The demographic characteristics are described in Table 1.

Table 2. Types of cutaneous adverse events, grades, and clinical progression

Type of cutaneous reaction	n(%)	Onset (median (IQR)), weeks	Improvement n(%)	Time Taken for Improvement (median (IQR)), weeks	Resolved reactions n(%)	Time Taken for Resolution (mean ± SD), weeks
Xerosis	33 (21.7)	4 (2)	21 (63.6%)	5 (4)	4 (12.1%)	6.3 (4.8)
Paronychia	25 (16.4)	4 (3)	11 (44.0%)	4 (6)	6 (24%)	16.5 (44)[a]
Nail toxicities[b]	19 (12.5)	8 (14)	4 (21.0%)	11.5 (15)	0 (0.0%)	-
Maculopapular rashes	12 (7.9)	5 (14)	9 (75.0%)	4 (5)	2 (16.7%)	2.5 (2.1)
Acneiform eruption	12 (7.9)	1 (3)	7 (58.3%)	4 (4)	1 (8.3%)	12
Hypopigmentation	10 (6.6)	5 (8)	1 (10.0%)	8	0 (0.0%)	-
PPES	8 (5.3)	4 (8)	5 (62.5%)	8 (4)	0 (0.0%)	-
Alopecia	5 (3.3)	8 (11)	1 (20.0%)	9	0 (0.0%)	-
Hair colour changes	5 (3.3)	4 (15)	0 (0.0%)	-	0 (0.0%)	-
Hyperpigmentation	4 (2.6)	6 (7)	1 (25.0%)	4	1 (25%)	40
Pruritus	3 (2.0)	3 (1)[c]	2 (66.7%)	10 (2.8)[c]	0 (0.0%)	-
Skin Atrophy	1 (0.7)	8[c]	0 (0.0%)	-	0 (0.0%)	-
Other CADRS	6 (3.9)	3.5 (3)	2 (33.3%)	4.5 (5.0)[c]	0 (0.0%)	-

PPES = Palmar-Plantar Erythrodysesthesia Syndrome; IQR = interquartile range

[a]median (IQR) in weeks; bNail toxicities include nail discoloration, ridging and nail loss; cmean (standard deviation) in weeks

Clinical Features of cADRs and Skin Care Practices

The most frequently encountered cADRs were xerosis (21.7%), followed by paronychia (16.4%), nail toxicities (12.5%), maculopapular rashes (7.9%) and acneiform rashes (7.9%) (Table 2). The most common culprit drug group was the EGFRI, accounting for 56.8% of patients with reactions, followed by multikinase inhibitors (33.6%) (Table 3). Among patients on EGFRI, the most common cADRs seen were paronychia (42.1%) and rashes (34.5%) (Table 4).

Table 3. Targeted therapy and cADRs events

	With CADRs	Without CADRs
EGFR Inhibitors, n(%)	50 (87.7)	7 (12.3)
Gefitinib, n(%)	23 (82.1)	5 (17.9)
Afatinib , n(%)	13 (100.0)	0 (0.0)
Osimertinib, n(%)	9 (81.8)	2 (18.2)
Panitumumab, n(%)	3 (100.0)	0 (0.0)
Cetuximab, n(%)	2 (100.0)	0 (0.0)
Multikinase Inhibitors, n(%)	25 (49.0)	26 (50.9)
Imatinib, n(%)	7 (31.8)	15 (68.2)
Pazopanib, n(%)	10 (83.3)	2 (16.7)
Sunitinib, n(%)	2 (25.0)	6 (75.0)
Lenvatinib, n(%)	3 (60.0)	2 (40.0)
Axitinib, n(%)	2 (100.0)	0 (0.0)
Sorafenib, n(%)	1 (50.0)	1 (50.0)
CDK 4/6 Inhibitors, n(%)	8 (50.0)	8 (50.0)
Palbociclib, n(%)	4 (50.0)	4 (50.0)
Abemaciclib, n(%)	2 (50.0)	2 (50.0)
Ribociclib, n(%)	2 (50.0)	2 (50.0)
VEGFR inhibitors		
Bevacizumab, n(%)	3 (25.0)	9 (75.0)
HER2 Inhibitors		
Trastuzumab, n(%)	2 (18.2)	9 (81.8)
ALK Inhibitors, n(%)	0 (0.0)	5 (100.0)
Alectinib, n(%)	0 (0.0)	3 (100.0)
Ceritinib, n(%)	0 (0.0)	1 (100.0)
Crizotinib, n(%)	0 (0.0)	1 (100.0)

EGFR=Epidermal growth factor; CDK=cyclin-dependent kinase; VEGFR=vascular endothelial growth factor; HER2=human epidermal growth factor receptor; ALK=anaplastic lymphoma kinase

Only 3 of the reported cADRs were of CTCAE grade 3 (severe or medically significant reaction) and above. None of the patients experienced severe cutaneous adverse reactions (SCAR) or life-threatening events such as anaphylaxis. All the reactions were not preventable.

Only 11 (7.1%) patients used sunscreen while 39 (25.7%) patients were on moisturizers. The use of sunscreen was significantly lower among patients with cADRs as compared to those without adverse reactions. (1.1% vs 15.2%, *p-value=0.002*).

Table 4. Targeted Therapies and common cADRs

Drug Classes	Commonest reactions (n,%)
EGFR inhibitor (n=57)	Paronychia (24, 42.1%) Xerosis (23, 40.3%) Acneiform eruptions (12, 21.1%) Maculopapular rashes (8, 14.0%)
Multi Kinase Inhibitors (n=51)	Hypopigmentation (20, 39.2%) Xerosis (7, 13.7%) PPES (5, 9.8%) Hair colour changes (5, 9.8%)
CDK Inhibitors (n=16)	Nail toxicities (4, 25.0%) Xerosis (2, 12.5%) Maculopapular rashes (2, 12.5%)
VEGF Inhibitors (n=12)	Xerosis (1, 8.3%) Maculopapular rashes (1, 8.3%)
HER2 Inhibitors (n=11)	Nail toxicities (2, 18.2%) Paronychia (1, 9.1%)

PPES=Palmar-Plantar Erythrodysesthesia Syndrome; EGFR = Epidermal growth factor; CDK = cyclin-dependent kinase; VEGFR = vascular endothelial growth factor; HER2 = human epidermal growth factor receptor; ALK = anaplastic lymphoma kinase

Risk Factors for cADRs

The presence of comorbidities, particularly hypertension, older age and a higher Eastern Cooperative Oncology Group (ECOG) performance scale were found to be significantly associated with the development of cutaneous events in this study. Cancer patients with comorbidities and ECOG more than 2 are 2.09 and 2.24 times more likely to have cADRs compared to their respective counterparts. However, multiple logistic regression analyses to determine independent risk factors for developing cADRs revealed no statistically significant results except for sunscreen use which is protective against cADRs with OR 0.09 (95% CI 0.01-0.91), *p=0.04*. (Table 5). The presence of liver disease, smoking, gender, ethnicity, and atopy history were not found to be significantly associated with the development of cADRs (Table 5).

Table 5. Risk factors associated with developing cADRs

Characteristics		n (%)	Crude OR (95% CI)	*p-value*	Adjusted OR (95% CI)	*p-value*
Age Group	**≥ 60 years**	77 (50.6)	Ref		Ref	
	< 60 years	75 (49.3)	1.64 (0.86-3.15)	0.66	1.63 (0.74-3.58)	0.23
Gender	**Male**	66 (43.4)	Ref		Ref	
	Female	86 (56.6)	0.92 (0.49-1.76)	0.79	1.65 (0.71-3.82)	0.24
BMI	**Normal (18.5-24.9)**	59 (38.8)	Ref		Ref	
	Underweight (<18.5)	31 (20.4)	1.06 (0.37-3.03)	0.91	1.26 (0.43-3.70)	0.68
	Overweight (25.0-29.9)	40 (26.3)	1.32 (0.41-4.27)	0.64	0.50 (0.19-1.35)	0.17
	Obese (>30)	19 (12.5)	0.66 (0.22-1.98)	0.46	1.13 (0.32-3.93)	0.85
Comorbidities	**No**	79 (52.0)	Ref		Ref	
	Yes	73 (48.0)	2.09 (1.08-4.04)	0.03	0.86 (0.11-6.79)	0.88
Diabetes	**No**	126 (82.9)	Ref		Ref	
	Yes	26 (17.1)	0.82 (0.35-1.92)	0.65	0.43 (0.13-1.46)	0.18
Hypertension	**No**	92 (60.5)	Ref		Ref	
	Yes	60 (39.5)	2.07 (1.05-4.08)	0.04	4.37 (0.60-31.93)	0.15
Heart Disease	**No**	148 (97.4)	Ref		Ref	
	Yes	4 (2.6)	0.72 (0.10-5.26)	0.75	1.10 (0.76-16.1)	0.94
Liver Disease	**No**	146 (96.1)	Ref		Ref	
	Yes	6 (3.9)	3.8 (0.43-33.3)	0.20	6.71 (0.35-128.21)	0.21
Dyslipidaemia	**No**	140 (92.1)	Ref		Ref	
	Yes	12 (7.9)	1.02 (0.31-3.37)	0.97	0.50 (0.11-2.40)	0.39
Renal impairment	**No**	148 (97.4)	Ref		Ref	
	Yes	4 (2.6)	0.45 (0.05-4.43)	0.44	1.10 (0.09-14.63)	0.94
Other comorbidities	**No**	133 (87.5)	Ref		Ref	
	Yes	19 (12.5)	0.6 (0.21-1.67)	0.32	1.82 (0.53-6.27)	0.34
ECOG	**Grade ≥2**	110 (72.4)	Ref		Ref	
	Grade <2	42 (27.6)	2.24 (1.04-4.82)	0.04	1.76 (0.69-4.50)	0.24
Lifestyle						
Smoking	**No**	132 (86.8)	Ref		Ref	
	Yes	20 (13.1)	1.83 (0.66-5.05)	0.24	2.47(0.70-8.68)	0.16
Moisturiser use	**No**	113 (74.3)	Ref		Ref	
	Yes	39 (25.7)	0.697 (0.34-1.45)	0.33	1.03 (0.40-2.68)	0.95
Sunscreen	**No**	142 (93.4)	Ref		Ref	
	Yes	10 (6.6)	0.07 (0.01-0.57)	<0.01	0.09 (0.01-0.91)	0.04
Atopy history	**No**	137 (90.1)	Ref		Ref	
	Yes	15 (9.9)	0.605 (0.21-1.76)	0.35	0.87 (0.23-3.28)	0.84
History of drug allergy	**No**	136 (89.4)	Ref		Ref	
	Yes	16 (10.5)	1.43 (0.51-4.03)	0.50	0.43 (0.12-1.60)	0.21
Family history of drug allergy	**No**	146 (96.1)	Ref		Ref	
	Yes	6 (3.9)	0.718 (0.14-3.68)	0.69	1.54 (0.19-12.84)	0.69
Number of drugs	**<3 Drugs**	113 (74.3)	Ref		Ref	
	≥3 Drugs	39 (25.6)	1.06 (0.51-2.22)	0.87	0.79 (0.32-1.97)	0.61

Odds ratio estimated using univariate and multivariate logistic regression model with significant p-value<0.05. OR = Odds ratio, CI = Confidence Interval, ECOG = Eastern Cooperative Oncology Group performance scale

Treatment and Outcome of cADRs

Most cADRs (84.6%) appeared within the first 2 months of targeted treatment. Most patients (84 patients, 93.2%) continued with their targeted therapy. Most of the cADRs (66.4%) showed improvement / resolution of symptoms within 4 to 8 weeks of onset (Table 2). Therapeutic intervention was required in 81.8% of patients with cADRs. The most frequently prescribed treatments were emollients (53 patients, 60.2%), followed by topical corticosteroids (39, 44.3%), systemic antibiotics (21 patients, 23.9%) and topical antibiotics (11 patients, 12.5%). Only 1 patient required systemic steroid therapy.

In patients who were on targeted therapy for at least 3 months, clinical and/or radiographical evidence of cancer progression was noted in 42 (47.7%) patients with cADRs as compared to 29 (45.3%) patients without cADRs.

Discussion

Targeted therapies inhibit specific molecular pathways that are central for tumour growth and survival. This selectivity allows the drug to deliver its therapeutic effect while reducing systemic side effects commonly associated with conventional chemotherapies. However, some of the signaling pathways are expressed in the epidermis, hair follicles and periungual area which are essential for normal skin physiology and barrier maintenance.[16] Consequently, inhibition of these pathways leads to development of numerous cutaneous side effects seen in patients on targeted therapy.

Previously, clinical studies on targeted therapies were done mainly on East Asian, United States and European population.[17–19]a third-generation epidermal growth factor receptor (EGFR Cutaneous reactions in these studies were reported using catch-all terms such as rashes or skin reactions. This study examines cADRs in a multi-ethnic Southeast Asian population, specifically evaluating the different types of cutaneous reactions among the different classes of targeted therapies used and their clinical pattern.

The prevalence of cADRs among oncology patients on targeted therapy in this study was 57.9%. Previous clinical studies have also similarly shown the frequency of cADRs ranging from 35.5% to 68%, depending on the type of agents used.[17,18,20,21]

The majority of cADRs seen were associated with the use of EGFRI. Paronychia was the commonest reaction seen (42.1%). This is in contrary to other studies where rash was the commonest symptom encountered (East Asia, 41.2-66.2%; United States, 49%).[17–23] This difference may be due to the heterogeneity of therapies and drug doses used among the various studies. Paronychia may initially manifest as nail fold inflammation and tenderness and may progress to granulation tissue growth with purulent discharge. Preventive measures include avoidance of repeated friction and diluted bleach soaks for digits while therapeutic treatment comprise of topical corticosteroids and tetracyclines.[24]

Xerosis was another common cutaneous reaction, seen in 40.3% of patients on EGFR inhibitors in this study. Previous studies have found incidences of xerosis to be between 28.9-35%.[19,20,25] Inhibition of EGFR is believed to affect basal keratinocytes via growth arrest, abnormal differentiation, and cell apoptosis. This leads to increased barrier dysfunction and also increased transepidermal water loss, resulting in skin dryness.[16] Xerosis usually happens around 1-2 months after initiation of treatment. Patients present with dry scaling skin that may often cause significant itching. These tend to occur at sites where papulopustular rashes previously developed. Preventive measures consist of avoidance of scrubbing and hot shower. Treatment should aim to rehydrate the skin and restore the skin barrier. Liberal moisturizer usage is highly encouraged and patients should be advised to pick skin care products that are free of fragrances and alcohol.[26]

Age, gender, atopy history and polypharmacy are established risk factors for cutaneous drug reactions.[27–30] In this study, only the presence of older age, comorbidities and poor ECOG

performance status (PS) grade 2 or more were found to be significantly associated with the development of cADRs. These findings were also similarly reported in previous studies.[29,31,32] Patients with these risk factors should be advised regarding prophylactic skin care, such as frequent application of moisturizers and avoidance of mechanical trauma. They should also be closely monitored for cutaneous reactions during routine follow up. Early identification and treatment of cutaneous adverse events in these patients may prevent progression into more severe complications.

The use of sunscreen was found to have a protective effect on the development of cADRs in our study population. This finding was similarly seen in a study by Lacouture *et al* on patients on panitumumab.[33] This protective effect of sunscreen may be explained by the fact that ultraviolet (UV) radiation may trigger cutaneous reactions via UV-induced apoptosis of keratinocytes.[34–36] Further studies are needed to assess the effect of prophylactic application of topical sunscreen for the prevention of cADRs.

Topical moisturizers have been advocated as prophylactic therapy in preventing the development of cADRs.[37,38] Lacouture et al used a preventive regime consisting of sunscreen, moisturizers, topical steroids and oral doxycycline for patients receiving panitumumab and found 50% reduction in grade ≥2 cutaneous reactions compared to patients on reactive treatment.[33] However, in this study, we did not find any significant association between the use of moisturizers with the development of cADRs.

Current guidelines on the management of cADRs favour the use of supportive treatment for mild to moderate cADRs, and the withdrawal of targeted therapy for severe reactions [24,37,38] The majority of our patients with cADRs developed mild grade cutaneous events while no severe cutaneous adverse reactions (SCAR) cases were reported. Most patients experienced improvement or resolution of symptoms with supportive care and did not require treatment discontinuation. This emphasizes that targeted therapy is not only a treatment with superior efficacy compared to conventional chemotherapy but is also safe and well tolerated. A good pre-treatment counselling on the expected reactions and preventive measures would therefore improve compliance in patients.

Previous studies have shown that the development of cADRs predicts better responses to targeted therapy, with improved overall disease survival and progress-free survival.[19,39–43] However, we did not identify such association in our study. This could be because most of our patients were already at an advanced stage of cancer during commencement of the targeted therapy and therefore had a very poor prognosis from the start.

The limitations of this study include a single-center study with a small sample size for each drug group.

Conclusion

Cutaneous adverse drug reactions are common among oncologic patients on targeted therapy, with a prevalence rate of 57.9% in this study. The most observed cADRs were xerosis and paronychia, and the commonest culprit drug group was the EGFRI. Most cADRs were of mild to moderate severity, requiring symptomatic therapy only without treatment interruption. Patients with concurrent comorbidities and worse ECOG performance score were more likely to develop cADRs. Sunscreen use may be beneficial in preventing cADRs. Knowledge on the prevalence and potential cutaneous side effects of oncologic treatment will help in early recognition and treatment of cADRs, thus leading to better treatment compliance. Combined management by dermatologists and oncologists can help reduce treatment-related morbidity.

Conflict of Interest Declaration

The authors have no conflict of interest to declare.

Acknowledgement

The authors would like to thank the Director General of Health, Malaysia for permission to publish this paper, Dr Lim Chun Sen, the Head of Department of Oncology, Hospital Sultan Ismail, Malaysia and Puan Aisyah binti Ali from the Clinical Research Center, Hospital Sultan Ismail, Malaysia for their support in facilitating this study.

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ORIGINAL ARTICLE

The Psychosocial Impact of Paediatric Atopic Dermatitis on Family

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Abstract

Background

Atopic dermatitis (AD) is a chronic pruritic inflammatory skin disease usually beginning in childhood. It affects the quality of life (QOL) of children as well as social and emotional functioning of their families. The aim of our study was to determine the association between severity of paediatric atopic dermatitis and the quality of life and mental health of caregivers.

Methods

One hundred caregivers of children with AD attending the Dermatology Clinic at Hospital Tengku Ampuan Rahimah Klang, participated in the study. The severity of AD was estimated using the Scoring Atopic Dermatitis (SCORAD) index. Caregivers were asked to answer a set of questionnaires consisting of Sociodemographic, Dermatitis Family Impact (DFI), and 9-item Patient Health Questionnaire (PHQ-9) during the visit.

Results

QOL of caregivers using DFI was significantly associated with the SCORAD score (*p= 0.033*), however depression score and monthly financial assessment were not significantly associated with SCORAD, *p=0.169* and *p=0.240* respectively. None of the demographic data significantly contributed to QOL of caregivers.

Conclusions

AD in children appeared to have a significant impact on the quality of life of caregivers. There was no significant impact on mental health.

Key words: *Atopic dermatitis, quality of life, depression*

Introduction

Atopic dermatitis is the commonest skin disease in children. It is a chronic disease and persistent itch leads to chronic sleep disruption, contributes to a child's lack of sleep which causes functional, emotional, behavioural problems, and delayed physical and social development.[1] Caregivers of children with AD report exhaustion, frustration, and mood disorders.[2-4] Sleep disturbances were directly associated with severity of atopic dermatitis and parents reported that the atopic

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dermatitis affected the child and family's happiness.[2]

Physicians tend to focus on physical aspects of AD and neglect the psychosocial aspect, hence family impact is underestimated.[5] The quality of life of families of children with eczema is significantly poorer than that of families with healthy children.[6-8] In addition, a higher family impact or poorer quality of life are associated with increased eczema severity.[6,8,9] Parents of children with a higher severity of disease reported a significantly higher impact on family functioning and a greater financial burden, and differences attributed to their child's gender or age were not observed.[7]

A local study by *Aziah et al.* confirmed that the family impact and QOL were shown to be significantly greater in severe AD compared to moderate and mild AD. The parental score of DFI was 5.2 in mild atopic dermatitis, 8.5 in moderate atopic dermatitis and 11.5 in severe atopic dermatitis. The high impact domains of the family QOL in atopic dermatitis were family diet restriction, parental sleep loss, psychological pressure, and exhaustion.[8] Another local study conducted in Kelantan by *Ahmad Abir et al*. reported that for every 1 unit increase in disease severity score (SCORAD), there is 0.14 unit increase in Dermatitis Family Index score (DFI).[10]

A Singaporean study reported that family life was affected by their children's disease, with commonly affected domains of sleeping disturbance, emotional distress and exhaustion, while children's age, severity and duration of AD were factors contributing to negative impact on QOL.[11] This was a large study of children less than 16 years old. Several studies abroad done in UK[6], Croatia[12] and Saudi Arabia[13,14] also found that family QOL was significantly affected by severity of a child's AD.

Several studies in western countries found that there was significant association between the mental health of caregivers and severity of child's AD. *Moore K et al* found that caring for a child with chronic atopic eczema was significantly associated with greater parental sleep disturbances and disruption to parental sleep correlated with higher depression scores [15]. *Faught J et al* reported that mothers of children aged 5 years or less with eczema exhibited significantly higher total stress scores as compared to mothers of normal children or children with other chronic disorders such as insulin-dependent diabetes.[16] Caring for a child with AD leads to high levels of parental worry, sleep disruption, exhaustion, and family strain.[17] *Warschburger P et al.* also found that childhood AD has a profound impact on the emotional and social well-being of many of the parents, but not physical health. The results indicate that caring for a preschool child with AD adversely affects the mental health status of mothers.[7] This highlights the need for psychosocial support for caregivers of children with AD.

The financial burden of AD can extend beyond the direct costs of healthcare expenses. Additional costs also needed for transportation, home environment changes, homeopathic or alternative treatments, and work productivity losses. A study done in Australia suggested that direct financial cost for a child with moderate or severe eczema is substantially higher than for a child with asthma.[18] Apart from the direct financial costs, several factors that may have contributed to the higher impact on family scores, such as time taken to care for the child, time off work, and interruption to employment.[18]

In view of very few studies was conducted locally to explore the quality of life, mental health of caregivers of children with AD, and financial impact to family, our study aims to investigate these aspects.

Materials and Methods

A cross sectional study was conducted at Dermatology Clinic, Hospital Tengku Ampuan Rahimah Klang (HTAR), Selangor. One hundred main caregivers of paediatric patients diagnosed with Atopic Dermatitis fulfilling Hanifin and Rajka criteria[19](Table 1), were screened and recruited through convenience sampling from November 2021 to May 2022. We included

main caregivers aged 18 and above, of our paediatric patients who were below 18 years old. We excluded main caregivers who were (i) suffering from chronic medical illness(es), (ii) looking after immediate family members who suffered from chronic medical illness(es), or (iii) had underlying psychiatric disorder or other chronic illness(es) besides AD.

Table 1. Hanifin and Rajka diagnostic criteria for atopic dermatitis[19]

Must have≥ 3 major and ≥3 minor criteria for diagnosis of AD

Major
- Pruritus
- Typical morphology and distribution:
  -flexural lichenification or linearity in adults
  -facial and extensor involvement in infants and children
- Chronic or chronically relapsing dermatitis
- Personal or family history of atopy (asthma, allergic rhinitis, atopic dermatitis)

Minor
- Xerosis
- Ichthyosis/palmar linearity/keratosis pilaris
- Immediate (type 1) skin test reactivity
- Elevated serum IgE
- Early age of onset
- Tendency towards cutaneous infections (esp. Staphylococcus aureus and Herpes simplex)/impaired cell mediated immunity
- Tendency towards nonspecific hand and foot dermatitis
- Nipple eczema
- Cheilitis
- Recurrent conjunctivitis
- Deannie-Morgan infraorbital fold
- Keratoconus
- Anterior subcapsular cataract
- Orbital darkening
- Facial pallor/facial erythema
- Pityriasis alba
- Anterior neck folds
- Itch when sweating
- Intolerance to wools and lipid solvents
- Perifollicular accentuation
- Food intolerance
- Course influence by environmental/ emotional factors
- White dermographism/delayed blanching

Questionnaires consisted of sociodemographic data, Dermatitis Family Impact (DFI) and 9-item Patient Health Questionnaire (PHQ-9) respectively were answered by the participants. Both DFI and PHQ0-9 questionnaires are validated. Sociodemographic data consisted of age, gender, educational level, working status and monthly family income. DFI had a total score 30 and 0–5 was classified as normal, 6–10 as minor alteration, 11–20 as moderate and >20 as high alteration. PHQ-9, based on DSM-IV, on participants experience for the past 2 weeks, had a total score of 27, and the range 0-4 were classified as none, 5-9 as mild, 10-14 as moderate, 15-19 as moderately severe and 20-27 as severe.

Severity of patients' AD were assessed by the treating doctor using SCORing Atopic Dermatitis (SCORAD). Scores ranging from 0 to <25 were classified as mild, 25 to 50 as moderate and >50 as severe. The maximum score is 103.

This study was approved by Medical Research and Ethical Committee (MREC), Malaysia with research code NMRR-21-1439-59865. Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS Version 28.0, IBM Corp). Chi square test and Fisher exact test were used for categorical data to examine any association between SCORAD, DFI and PHQ-9. The significance level was set at $p<0.05$. ANOVA test was used for continuous variables and were summarized as mean and standard deviation (SD). Results were significant for $p< 0.05$.

Results

Characteristics of Participants (main caregivers)

A total of 100 caregivers of children with AD were enrolled in this study. The sociodemographic characteristics of caregivers and children with atopic dermatitis were shown in Table 2. Most of the caregivers were aged 30 to 40 years old, comprised of mothers (86.0%), of Malay ethnicity (91.0%) and were married (96.0%). Majority had tertiary education (55.0%) and working full time (56.0%). Most of the subjects had a household income of RM 3000 to RM

4999, with number of children between 2 to 3, without of domestic helper. Majority of the patients aged 0 to 4, with a mean age of 5.4 years.

SCORAD of Children with atopic dermatitis

The SCORAD scores of the study children are shown in Figure 1. Majority of the children had moderate AD (70.0%), followed by mild AD (25.0%) and severe AD (5.0%). Our mean SCORAD was 30.86.

Quality of life and depression measurements of caregivers

Dermatitis Family Index (DFI) was used to measure QOL of caregivers and depression was measured with Patient Health questionnaire- 9 (PHQ-9). Majority of our subjects, 77 caregivers out of 100 subjects had normal DFI score, which showed no alteration in quality of life. 10 had minor alteration in quality of life while 13 had their quality of life moderately affected, as shown In Table 3. Based on AD severity, for mild AD group, 96.0% had normal DFI, only 4.0% had moderate DFI, whereas in moderate AD group, 14.3% had moderate DFI and in severe AD group, 40.0% had moderate DFI. None had severely affected DFI. DFI was significantly associated with SCORAD (*p=0.033*). The mean age of children was 6.12 years for caregivers with normal DFI, followed by 2.08 for mild DFI group and 3.59 for moderately affected DFI group of caregivers.

Figure 1. SCORAD of children with atopic dermatitis

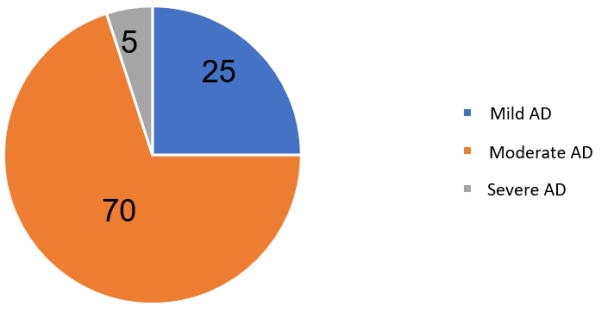

Table 2. Sociodemographic characteristics of the caretakers and children with atopic dermatitis

Characteristic	Frequency (%)
Caretaker's age (years)	
<30	26 (26.0)
30-40	53 (53.0)
40-45	18 (18.0)
>50	3 (3.0)
Gender	
Male	14 (14.0)
Female	86 (86.0)
Race	
Malay	91 (91.0)
Chinese	4 (4.0)
Indian	3 (3.0)
Others	2 (2.0)
Marital status	
Married	96 (96.0)
Divorced	2 (2.0)
Widow/Widower	1 (1.0)
Not married	1 (1.0)
Educational status	
No	1 (1.0)
Primary	3 (3.0)
Secondary	41 (41.0)
Tertiary	55 (55.0)
Working status	
Not working	43 (43.0)
Part time	1 (1.0)
Full time	56 (56.0)
Monthly family income	
<1000	3 (3.0)
1000-2999	29 (29.0)
3000-4999	42 (42.0)
≥5000	26 (26.0)
Number of kids	
1	24 (24.0)
2	27 (27.0)
3	27 (27.0)
4	12 (12.0)
≥5	10 (10.0)
Domestic helper	
Yes	1 (1.0)
No	99 (99.0)
Age of child	Mean age: 5.40
0-4	56 (56.0)
5-10	23 (23.0)
11-17	21 (21.0)

Table 3. DFI scores of caretakers of children with atopic dermatitis based on SCORAD

Variable	DFI			*p value*
	Normal n (%)	**Minor n (%)**	**Moderate n (%)**	
SCORAD				***0.033***
Mild	24 (96.0)	0 (0.0)	1 (4.0)	
Moderate	50 (71.4)	10 (14.3)	10 (14.3)	
Severe	3 (60.0)	0 (0.0)	2 (40.0)	
Total (n=100)	77 (77.0)	10 (10.0)	13 (13.0)	
Mean (SD) age	6.12 (4.76)	2.08 (2.30)	3.59 (4.92)	

Fisher's exact test

Table 4 shows that most of the caregivers (85.0%) had no depression, 12 had mild depression and 13% had moderate depression. For mild AD group, 100.0% had no depression, whereas in moderate AD group, 85.9% had no depression, 11.5% had mild depression and 2.6% had moderate depression while in severe AD group, 27.3% had mild depression and 9.1% has moderate depression. None had severe depression. However, there was no statistically significant association between depression and SCORAD (*p= 0.169*). The mean age of children were 5.78 years for caregivers with no depression, followed by 3.23 for mild depression group and 2.97 for moderate depression group of caregivers.

Table 4. PHQ-9 scores of caretakers of children with atopic dermatitis based on SCORAD

Variable	PHQ-9			*p value*
	None n (%)	**Mild n (%)**	**Moderate n (%)**	
SCORAD				*0.169*
Mild	11 (100.0)	0 (0.0)	0 (0.0)	
Moderate	67 (85.9)	9 (11.5)	2 (2.6)	
Severe	7 (63.6)	3 (27.3)	1 (9.1)	
Total (n=100)	**85 (85.0)**	**12 (12.0)**	**3 (3.0)**	
Mean (SD) age	5.78 (4.88)	3.23 (3.43)	2.97 (4.45)	

Fisher's exact test

Table 5 shows the mean value of SCORAD, Objective SCORAD, itch and sleep in each category of DFI severity. Total SCORAD, Objective SCORAD and sleeplessness score was highest in Moderate DFI group with 39.03, 30.88 and 3.62 respectively. Mean SCORAD was 30.82. Itch score was equally high in both minor and moderate DFI group with 4.6 and 4.46 respectively.

Table 5. Association between DFI with Total SCORAD, Objective SCORAD Itch and Sleep

		DFI		*p value*
Scores	**Normal Mean (SD)**	**Minor Mean (SD)**	**Moderate Mean (SD)**	
Total SCORAD (Mean: 30.82)	29.08 (8.51)	33.90 (6.54)	39.03 (10.26)	*0.033*
Objective SCORAD	22.76 (7.08)	26.0 (4.40)	30.88 (6.72)	
Itch	3.56 (1.63)	4.6 (2.63)	4.46 (2.50)	
Sleep	2.77 (1.43)	3.3 (2.16)	3.62 (2.40)	

Table 6 shows DFI domains. Highest scoring DFI domains were sleep disturbance (0.63±0.91) and expenditure (0.63±0.79), followed by exhaustion (0.49±0.79) and housework (0.47±0.76).

Table 6. Family Dermatology Life Quality Index domains

Item	Range	Mean+ SD
Total	0-30	3.98 + 4.84
Housework	0-3	0.47 + 0.76
Diet	0-3	0.35 + 0.64
Sleep disturbance	0-3	0.63 + 0.91
Leisure activities	0-3	0.35 + 0.74
Shopping	0-3	0.25 + 0.61
Expenditure	0-3	0.63 + 0.79
Exhaustion	0-3	0.49 + 0.79
Emotion	0-3	0.37 + 0.65
Relationship	0-3	0.04 + 0.20
Effort in helping	0-3	0.40 + 0.70

Factors contributing to quality of life

Table 7 shows factors contributing to caregivers' QOL. None of the demographic variables of caregivers or age of patient significantly affected DFI ($p<0.05$). Thus, these demographic variables did not significantly contribute to quality of life of caregivers.

Table 7. Factors contributing to caretakers quality of life (n=100)

Variable	Dermatitis Family Index				*p value*
	Normal	Minor	Moderate	Total	
Caretaker's age (years)					*0.540*
<30	18 (69.2)	5(19.2)	3 (11.5)	26	
30-40	40 (75.5)	5 (9.4)	8 (15.1)	53	
40-45	16 (88.9)	0 (0.0)	2 (11.1)	18	
>50	3 (1.0)	0 (0.0)	0 (0.0)	3	
Gender					*0.408*
Male	9 (64.3)	2 (14.3)	3 (21.4)	14	
Female	68 (79.1)	8 (9.3)	10 (11.6)	86	
Race					*0.078*
Malay	71 (78.0)	10 (11.0)	10 (11.0)	91	
Chinese	4 (100.0)	0 (0.0)	0 (0.0)	4	
Indian	2 (66.7)	0 (0.0)	1 (33.3)	3	
Others	0 (0.0)	0 (0.0)	2 (100.0)	2	
Marital status					*0.226*
Married	75 (78.1)	10 (10.4)	11(11.5)	96	
Divorced	1 (50.0)	0 (0.0)	1(50.0)	2	
Widow/ Widower	1 (100.0)	0 (0.0)	0 (0.0)	1	
Not married	0 (0.0)	0 (0.0)	1 (100.0)	1	
Educational status					*0.316*
No	0 (0.0)	0 (0.0)	1 (100.0)	1	
Primary	3 (100.0)	0 (0.0)	0 (0.0)	3	
Secondary	34 (82.9)	4 (9.8)	3 (7.3)	41	
Tertiary	40 (72.7)	6 (10.9)	9 (16.4)	55	
Working status					*0.173*
Not working	36 (83.7)	1 (2.3)	6 (14.0)	43	
Part time	1 (100.0)	0 (0.0)	0 (0.0)	1	
Full time	40 (71.4)	9 (16.1)	7 (12.5)	56	
Monthly family income					*0.376*
<1000	2 (66.7)	0 (0.0)	1 (33.3)	3	
1000-2999	24 (82.8)	1(3.4)	4 (13.8)	29	
3000-4999	34 (81.0)	4 (9.5)	4 (9.5)	42	
>5000	17 (64.4)	5 (19.2)	4 (15.4)	26	
Number of kids					*0.508*
1	19 (79.2)	4 (16.7)	1 (4.2)	24	
2	21 (77.8)	3 (11.1)	3 (11.1)	27	
3	18 (66.7)	3 (11.1)	6 (22.2)	27	
4	11 (91.7)	0 (0.0)	1 (8.3)	12	
>5	8 (80.0)	0 (0.0)	2 (20.0)	10	
Domestic helper					*1.000*
Yes	1 (100.0)	0 (0.0)	0 (0.0)	1	
No	76 (76.8)	10 (10.1)	13 (13.1)	99	
Child's age					*0.143*
0-4	38 (67.9)	8 (14.3)	10 (17.9)	56	
5-10	20 (87.0)	2 (8.7)	1 (4.3)	23	
11-17	19 (90.5)	0 (0.0)	2 (9.5)	21	

Fisher's exact test

Monthly expenses of children with AD

Caregivers of children with mild AD spent additional monthly expenses of RM 62.73 in average, followed by RM 80.86 and RM 127.27 in moderate to severe AD respectively, as shown in Table 8. There was no significant association between monthly expenses and severity of AD.

Table 8. Monthly expenses of children with atopic dermatitis according to SCORAD

Variable	n	Mean (IQR)	*p value*
SCORAD			*0.083*
Mild	25	62.73 (52.36)	
Moderate	70	80.86 (71.82)	
Severe	5	127.27 (87.65)	

ANOVA; IQR (Inter-quartile range)

Discussion

This study assessed QOL of caregivers of children with AD and the impact on caregivers' mental health, a subject that has not been adequately studied. We found that, there was significant association between severity of paediatric AD and the QOL of caregivers. Our results showed that AD had minor to moderate impact on QOL of caregivers of children with moderate to severe AD. For children with mild AD, majority of their caregivers had normal DFI, while those with moderate and severe AD, higher numbers of caregivers had moderately affected DFI. These findings corresponding to several similar studies done locally and internationally[6,8,11,19,20,22] which found that QOL was significantly associated with severity of AD.

Our study findings were similar to a local study done in Kuala Lumpur by *Aziah et al,* which found that the family QOL were shown to be significantly associated with severity of AD[8]. Their patients had almost similar mean age (6.2) as our patients (5.4). Majority of subjects in both our study and *Aziah et al* study was of Malay ethnicity. Their AD severity was also assessed using SCORAD. However, majority of the patients in our study had mild to moderate AD compared to moderate to severe eczema in their study. Sleep disturbance and exhaustion was

among the highest scoring domain reported in our study, were also the main domains reported by *Aziah et al*.

In our study, majority of our caregivers (77%) had normal DFI. This group of caregivers were parents of older children with AD (mean age 6.12) as compared to those with minor to moderate DFI who had younger kids with AD. This may be explained by the fact that younger children may need higher parental care that directly affect parent's QOL.

Another local study conducted in Kota Bharu, Kelantan by *Ahmad Abir et al.* also supported that QOL of family was significantly associated with AD severity. It was reported that for every 1 unit increase in disease severity score (SCORAD), there were 0.14 unit increase in impact of disease on family score (DFI). This study had similar disease severity spectrum as in our study where majority (two third) of the children suffered from moderate AD and one third had mild AD and only around 6% had severe AD[10], and majority caregivers (over 90%) were of Malay ethnicity as in our study. However, this study recruited older age group of 5 to 17 years old and excluded those below 5 years old, and caregivers were of lower income and lower education level, mainly up to secondary school, as opposed to our caregivers where most had tertiary education.

Several studies done abroad also found that AD severity had significant impact in QOL of family. A Singaporean study reported that family life was affected by their children's disease, with commonly affected domains of sleeping disturbance, emotional distress, and exhaustion, almost similar to the common domains found in our study. However, children's age was found to be one of the factors contributing to negative impact on QOL which was opposed to our study that found that age of children was not a significant contributing factor.[11] In contrast, EASI score was used, different AD severity SCORING system as our study, and they only included children with moderate to severe AD.

Another study done at primary care setting at London, UK reported that family QOL was related to the severity of AD in children[6], but the study only involved older children 5 to 10 years old with mean age of 8. Another study done at Croatia by *Pustišek N et al* also found that family QOL was significantly correlated with the SCORAD index, itching, sleep disturbance, as in our study.[12] Even though this study had larger sample size of 171, the children age group ranging from 3 months to 7 years old only while our study comprised of larger range of age up to 17 years old. Another 2 studies done in Saudi Arabia[13,14] showed that DFI score of parents of children with severe AD was significantly higher as compared to mild and moderate AD. The highest scoring DFI domains were expenditure and sleep disturbance, which were also similar to the main domains in our study. Majority of children AD were mild to moderate AD, almost similar to the AD severity spectrum as in our study. This further implies that parental quality of life assessment is important, and DFI questionnaire could be used as an extra measure of outcome in everyday clinical practice as well as in research studies.

With regards to mental health of caregivers, the was no significant association between depression and AD severity. Majority of caregivers had no depressive symptoms. However, 12 caregivers had mild depression and 3 had moderate depression. All these were caregivers of children with moderate to severe AD. We referred these participants to the psychiatrist for further assessment and management. None of the caregivers had severe depression. For children with mild AD, majority of their caregivers had no depression, while those with moderate and severe AD, higher numbers of caregivers had moderate depression. For the group with no depression, the mean age of children was 5.78, however those with mild to moderate depression, the children were younger with a mean age of 3.23 and 2.97 respectively. This could be explained that younger age group children needed higher level of care hence caused more psychological stress to parents. Parents of young children with AD can be particularly burdened because of the lack of sleep and the emotional stress of seeing their

child's distress. The non-statistical significance between depression and AD severity most likely because caregivers was adequately counselled and had better understanding about their child's illness, which creates less anxiety and worries. In view of AD is a chronic disease, most of the caregivers would have had adequate coping mechanisms.

Our study finding was opposed to the study by *Moore K et al* that found that caring for a child with chronic atopic eczema was significantly associated with greater parental sleep disturbances and disruption to parental sleep correlated with higher depression scores. However, the AD patients had moderate to severe AD, as mild AD were not included in the study, whereas in our study, majority of AD patient had mild to moderate AD. Hence this could explain the significant association found in their study. A study done in Beijing, China by *Su W et al* also found that factors associated with caregivers' depression symptoms included taking care of children with moderate and severe AD and not the mild AD group[23]. This study had a larger sample size of 901 subjects, which included children from 2 to 18 years old. However, the number of children with severe AD was three times higher compared to our AD children. This may explain the non-significant association between depression in caregivers and severity of paediatric AD most likely due to our smaller sample size and fewer number of severe AD children in our study.

None of the demographic variables were found to be significantly contributed to the impairment in quality of life. Age of children was not found to be a contributing factor. This was supported by *Warschburger P et al* study[7] that found that age was not a contributing factor to family QOL, as opposed to the Singaporean study.[11]

Concerning the association of family expenditure for AD with AD severity, these was no significant impact on monthly expenses, as most of the medications can be obtained from government hospitals. Only a minority of parents spent to purchase additional creams or body shampoo specifically for sensitive skin. This opposed to the findings in previous study by *Su W et al,* that showed that costs have been found to relate directly to eczema severity and were comparable to or greater than other chronic diseases of childhood such as asthma and diabetes[18]. However, this study was conducted overseas, which has a different clinical setting.
It is evident that assessment of QOL of caregivers of children with AD, and the recognition and understanding of the factors that affect QOL of caregivers are important for clinicians, to help reduce the impact of AD on both children and their caregivers. Mental health assessment is important for caregivers of AD children, especially in those with moderate to severe AD and the younger age group.

Limitations
Cautious interpretation of the results is needed, as the present study has some limitations. First, it was based on a rather small sample size via convenience sampling. During this period of Movement Control order (MCO), due to COVID pandemic, there were limited number of children who visited this clinic due to the fear of COVID. Other than that, mild and moderate cases of AD that were manageable by the general paediatric clinic in our hospital were not referred to us.

As most of the children in our study had mild to moderate AD, and only a few had severe AD, hence this may explain the reason that the caregivers were not severely affected in terms of DFI and depression aspect. Our skewed data was part of the limitations.

Conclusion

Our study found significant association between severity of paediatric AD and the QOL of caregivers. However, there was little impact on mental health. The management of AD in children should include multidisciplinary intervention, with the provision of psychoeducational programs for parents, to provide them with systematic and accurate information on characteristics and management of AD, along with QOL and mental health assessment, and

emotional support, to reduce negative impact on quality of life and depression in caregivers.

Conflict of Interest Declaration

The authors have no conflict of interest to declare.

Acknowledgement

We would like to thank the Director of General of Health Malaysia for his permission to publish this article.

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ORIGINAL ARTICLE

Transepidermal Water Loss, Stratum Corneum Hydration and Skin pH in Mild Chronic Plaque Psoriasis and the Association with Pruritus

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Abstract

Background

Epidermal barrier dysfunction within psoriatic plaques and uninvolved psoriatic skin has been reported in the literature but are not well researched. We aimed to determine the epidermal barrier properties among our mild psoriasis patients and investigate its association with pruritus.

Methods

A single centre, cross-sectional study involving mild psoriasis patients aged ≥18 years were carried out in Dermatology Clinic, Hospital Canselor Tuanku Muhriz (HCTM) between July to October 2022. Patients on systemic therapy, phototherapy and breast feeding were excluded. Clinical baseline demographics and characteristics were obtained by face-to-face interview. Physician Global Assessment (PGA) were utilized to determine psoriasis severity. Transepidermal water loss (TEWL), stratum corneum hydration and skin pH were measured at the psoriatic plaques and uninvolved psoriatic skin. Pruritus was measured using visual analog score (VAS) of 1-10.

Results

A total of 41 mild chronic psoriasis patients were enrolled in this study. The majority were male and Malays; n=26 (63.4%) and n=25 (61%) respectively. 29 patients (70.7%) had a longer disease duration of more than 10 years. Comparison between psoriatic plaques and uninvolved skin showed higher TEWL [mean difference= 9.25, 95% CI (6.64, 11.84), $p<0.001$], and higher skin pH [mean difference=0.49, 95% CI (0.19, 0.79), $p=0.002$] at the plaques. The stratum corneum hydration was lower in the psoriatic plaques [mean difference -57.78, 95% CI (-68.09, -47.46), $p<0.001$]. There were no significant association between pruritus and the measured epidermal barrier parameters at both the psoriatic plaques and the uninvolved psoriatic skin.

Conclusion

Skin barrier dysfunction was observed within psoriatic plaques. TEWL and pH were higher while the stratum corneum hydration was lower in psoriatic plaques compared to uninvolved skin. The abnormalities in these biophysical parameters were not associated with pruritus intensity.

Key Words: *Plaque psoriasis, transepidermal water loss, stratum corneum hydration, skin barrier*

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Introduction

Psoriasis is an immune-mediated chronic inflammatory skin disease with prevalence of 0.14% in East Asia to 1.99% in Australasia.[1] Pathophysiology of psoriasis includes accelerated epidermal proliferation, abnormal keratinocyte differentiation, increased angiogenesis and immune dysregulation.[2,3] Advances in psoriasis therapy in recent years are focused on modulation of the immune system

for disease control. Changes in epidermal barrier characteristics and functions are well described in atopic eczema. These changes guide development of topical therapies. Similar changes have been described in psoriasis. Hyperproliferation and defective keratinocyte differentiation in psoriasis further impaired the epidermal barrier function.

Epidermal barrier function can be assessed objectively by transepidermal water loss (TEWL), the stratum corneum hydration, sebum production and skin pH. In the literature, TEWL were reported higher in the psoriatic plaques and uninvolved psoriatic skin compared to healthy normal skin. The stratum corneum hydration however were reduced in psoriatic plaques than uninvolved psoriatic skin.[4-7] Regarding the skin pH, it was reported to be slightly lower in psoriatic plaques compared to uninvolved psoriatic skin and significantly lower than healthy controls.[5] Sebum and pH in psoriasis skin are less well studied.

There was an impact on different formulation to the epidermal barrier function. Application of occlusive moisturizer will reduce TEWL however on contrary, TEWL will be increased with a water-based moisturizer in addition to skin hydration.[5] Knowledge in epidermal biophysical characteristics of psoriasis may direct further formulations of topical therapy.

Pruritus is a common yet under-recognized symptom of psoriasis. Pruritus affects up to 60-90% of patients, especially females and smokers.[6-11] Pruritus contributes to sleep disturbance and has an additional negative impact on the quality of life of psoriasis patients.[6-10] The mechanism of itch is complicated. Neuropeptides, opioid receptors, immune cells, various cytokines, corticotropin-releasing and α-melanocyte-stimulating hormones, prostaglandin, endothelin and abnormal keratinocyte proliferation are involved in the pathophysiology of itch.[12] Severe itch occurs when lesion appear or psoriatic plaque expand, and significant relief from pruritus is generally associated with resolution of the psoriatic lesions.[11] There is lack of data on the effect of abnormal epidermal biophysical properties on itch in psoriasis. Knowledge on the relationship between epidermal dysfunction and itch will help better management strategies for controlling itch in patients with psoriasis.

The objective of this study was to determine the transepidermal water loss, stratum corneum hydration and skin pH in patients with psoriasis, and to evaluate the association of these skin parameters with symptom of itch. Transepidermal water loss, stratum corneum hydration and skin pH were compared between psoriatic plaques to uninvolved psoriatic skin.

Materials and Methods

Study design

A single centre, cross-sectional study was carried out at Dermatology Clinic, Hospital Canselor Tuanku Muhriz (HCTM) from July 2022 to October 2022. The eligible patients with mild psoriasis aged ≥18 years old were recruited via convenience sampling. We exclude patients with moderate to severe psoriasis, erythrodermic, pregnancy or breastfeeding, patients on immunosuppressant, biologics or phototherapy, other concomitant skin disease. Informed consent was obtained. The study protocol was approved by Research Ethic Committee of Universiti Kebangsaan Malaysia.

The baseline demographic and clinical characteristics including age, gender, ethnicity, disease duration, smoking status, body mass index (BMI) and current treatment including type of emollients were obtained from medical records and by interviewing the patients. The disease severity was assessed by Physician Global Assessment (PGA).

TEWL, stratum corneum hydration and skin pH were measured once the patient has been acclimatized to the environment of a dedicated room for 15 minutes. The average ambient air temperature of the room was 18^0C. All topical applications were stopped at least 4 hours prior to the measurements. A single investigator performed all the measurements for all the patients. TEWL in gm-^{2}.h-^{1} was measured

using Tewameter® TM 300, stratum corneum hydration (in arbitrary units using DermaLab Series SkinLab Combo (Z5010112UK) while skin pH was measured using Hanna HI 99181. Three measurements of each parameter were performed and the average was recorded. A single most representative psoriatic plaque on the upper and lower limb was selected for measurement of TEWL, stratum corneum hydration and skin pH. Measurements were performed at the center of the psoriatic plaque. The uninvolved psoriatic skin was defined as 3 cm away from the edge of the selected psoriatic plaque. Itch severity was evaluated by the patients using a visual analogue score where 0 represented no itch at all to a maximum of 10 for the worst itch ever experienced.

Statistical analyses

Data analyses were analysed using SPSS version 28. Characteristics of the study population were summarized from results of descriptive analysis. Frequencies and percentages were calculated for categorical variables. Continuous variables were expressed as mean and standard deviation as explorative analysis showed most variables were normally distributed. T-test determined differences in TEWL, SC hydration and skin pH between psoriatic plaque and uninvolved psoriatic skin. Paired samples T-test was used to examine the association between itch and the various skin biophysical measurements. *p*-value <0.05 was considered statistically significant.

Results

Characteristics of the study population

A total of 41 mild chronic psoriasis patients were recruited in this study. The mean age was 45.6±15.71 years. The mean body mass index (BMI) was 28.46 5.28 kg/m^2. The majority were Malays, 25 (61%), followed by Indian, 3 (7.3%) and Chinese, 13 (31.7%). There were 26 (63.4%) males and 15 (36.5%) females. Most of the patients; 29 (70.7%) has psoriasis for more than 10 years.

Topical therapy and emollients

All patients applied skin directed therapy using standard topical modalities which include emollients. Thirty-seven patients (90.2%) used topical corticosteroids and coal tar, 5 (12.2%) patients used topical calcineurin inhibitors while 2 (4.9%) patients used keratolytics.

Regarding the type of emollients, majority of our patients, 44 patients used water-based moisturizer; 32 (78.0%) patients applied aqueous cream and 2 (29.3%) patients applied 50% glycerin in aqueous cream. The remaining 6 patients were on occlusives; 5 (12.2%) patients used white soft paraffin, 3 (7.3%) patients used carbamide 10% cream and 1 (2.4%) patient used emulsificant ointment. Characteristics of the study population and the patients' current treatment are summarized in Table 1.

Table 1. Characteristics of the study population

Characteristics	**n=41 n (%)**
Age, mean±SD	45.66±15.71
Body mass index (BMI kg/m^2), mean±SD	28.46±5.28
Gender	
Male	26(63.4)
Female	15(36.6)
Ethnicity	
Malay	25(61.0)
Indian	3(7.3)
Chinese	13(31.7)
Duration of psoriasis, years	
<5	5(12.2)
>5-10	7(17.1)
>10	29(70.7)
Psoriasis severity, Physicians Global Assessment (PGA)	
Mild	41(100)
Current treatment	
Systemic therapy/ phototherapy	0(0.0)
Topical treatment	
Topical corticosteroid	37(90.2)
Topical calcineurin inhibitor	5(12.2)
Keratolytics	2(4.9)
Coal tar (Sebitar)	37(90.2)
Emollients	40(97.6)
Aqueous cream	32(78.0)
50% Glycerin in aqueous cream	12(29.3)
Emulsificant ointment	1(2.4)
White soft paraffin (vaseline)	5(12.2)
Carbamide 10% cream	3(7.3)

The relationship between TEWL, SC hydration and skin pH at the psoriatic plaques and uninvolved psoriatic skin

The epidermal barrier function parameters

were compared between psoriatic plaques and uninvolved psoriatic skin. In this study, there was a marked increase in TEWL at the psoriatic plaques compared to uninvolved psoriatic skin. The mean TEWL in psoriatic plaques were reported 16.01±8.50 and TEWL in uninvolved psoriatic skin were 6.76±2.37, $p<0.001$. The stratum corneum hydration was reduced in psoriatic plaques with a mean of 21.15±15.43 in comparison to 78.93±33.20 at the uninvolved psoriatic skin, p <0.001. Skin pH at the uninvolved psoriatic skin were lower than the psoriatic plaques. The mean pH measured on the psoriatic plaques were higher at 5.68±0.50 than the uninvolved psoriatic skin 5.19±0.95, $p=0.002$ Table 2.

The association between itch score and TEWL, SC hydration and skin pH at the psoriatic plaques and uninvolved psoriatic skin

Only 18 out of 41 patients complained of itch in this study. Itch score was categorized into 0-4 and 5-10 due to the small number of patients with itch. There were no significant associations between itch score and TEWL, stratum corneum hydration and skin pH at both psoriatic plaques and uninvolved skin as shown in Table 3.

Table 2. The relationship between TEWL, SC hydration and skin pH at the psoriatic plaques and uninvolved psoriatic skin

	Lesional Mean ± SD	Perilesional Mean±SD	Mean difference	95% CI	*p*-value
TEWL	16.01(8.50)	6.76(2.37)	9.25	(6.64, 11.84)	<0.001
SC Hydration	21.15(15.43)	78.93(33.20)	-57.78	(-68.09, -47.76)	<0.001
Skin pH	5.68(0.50)	5.19(0.95)	0.49	(0.19, 0.79)	0.002

Table 3. The association between itch and TEWL, SC hydration and skin pH at the psoriatic plaques and uninvolved psoriatic skin

Epidermal barrier parameters	Itch score 0-4	Itch score 5-10	Mean difference	95%CI	*p*-value
	Mean±SD	Mean±SD			
Lesional					
TEWL	15.41(8.07)	17.18(9.49)	-1.76	(-7.47, 3.94)	0.535
SC Hydration	22.26(16.05)	19(14.5)	3.26	(-7.1, 13.62)	0.528
Skin pH	5.64(0.55)	5.77(0.4)	-0.13	(-0.47, 0.21)	0.439
Perilesional					
TEWL	6.85(2.67)	6.61(1.75)	0.24	(-1.36, 1.84)	0.765
SC Hydration	80.81(31.43)	75.29(37.36)	5.53	(-16.8, 27.86)	0.619
Skin pH	5.05(1.05)	5.47(0.72)	-0.42	(-1.05, 0.21)	0.189

Discussion

Psoriasis is an inflammatory immune-mediated cutaneous disease resulting in hyperproliferation and defective keratinocyte differentiation[13] which resulted impaired skin barrier function. The epidermal barrier function can be measured objectively using non-invasive methods TEWL, stratum corneum hydration, skin pH, temperature, skin elasticity, melanin and erythema index[6] the four later paramaters were not included in this study. Data on these aspects of skin changes in psoriasis vulgaris are scarce in the literature. There is lack of data on the relationship between skin biophysical properties and symptom of itch.

Kelleher et al. reported that measurement of skin homeostasis and epidermal barrier function in psoriasis will help clinicians to assess the disease severity.[14] Impaired skin barrier was associated with increased TEWL, reduced stratum corneum hydration and lower skin pH.

Higher TEWL [6,17-18] and lower stratum corneum hydration[6] were associated with greater disease severity in psoriasis patients.

Our study findings were consistent with current knowledge in the pre-existing literature. TEWL within the psoriatic plaques were increased 2 to 20-fold compared with the uninvolved psoriatic skin in previous studies.[5-6,15-16] In our study, we demonstrated 2.3-fold increased TEWL in the psoriatic plaques compared to the uninvolved psoriatic skin. This study reported both epidermal barrier dysfunction in both psoriatic plaque and uninvolved psoriatic skin. This further supported by previous evidence that TEWL of skin unaffected by psoriasis were higher than normal skin of healthy volunteers.[6,7] Association between disease severity and TEWL levels was also demonstrated where higher TEWL correlated with more severe disease.[6,14-15] TEWL was similar among patients with or without psoriatic arthritis.[13]

We observed that stratum corneum hydration was lower in the psoriatic plaques compared to uninvolved psoriatic skin. Reduced hydration in psoriasis lesions compared to uninvolved psoriatic skin is a consistent finding reported in the literature.[4-5,15-16] The hydration in normal appearing skin in psoriasis patients were shown to be even significantly lower than the skin of the healthy volunteers in two previous studies.[5-6] The patho-mechanism postulated to explain the findings of TEWL and reduced hydration was the decrease in aquaporin 3 (AQP3) expression in psoriatic plaques compared to perilesional normal skin.[4] Skin hydration was lower in patients with PASI ≥7 versus those with PASI <7.[6]

Increased TEWL and reduced stratum corneum hydration on the psoriatic plaques are associated with skin barrier impairment. This advocates the use of moisturizer in the clinical management of psoriasis. The role of moisturizer in improving TEWL and skin hydration was investigated by Maroto-Morales et al.[5] Their findings support the potential clinical implication of the results of our study. The effects of Vaseline jelly with 100% mixture of semisolid hydrocarbons as ointment without excipients was compared with a water-based formula composed of emulsifier base NEO PCL O/W, distilled water, Phenonip ™ and glycerol. TEWL was observed to decrease by 5.59g/m^2 per hour, p=0.001 after application vaseline on the psoriasis plaques. TEWL increased significantly by 3.60g/m^2 per hour after application of the water-based formula. Similar changes were documented on skin unaffected by psoriasis but the difference was not significant with vaseline.[5] Stratum corneum hydration of both psoriasis plaque and skin unaffected by psoriasis increased significantly with the water-based moisturizer.[5]

There are very limited data on skin pH in psoriasis.[5,16,20] There is compelling evidence that epidermal pH can influence skin homeostasis and affect skin barrier by changing cutaneous enzyme and modulation of skin inflammation and microbial colonization. In addition, skin pH also affects the activity of the aquaporins which controls the skin hydration.[21] Keratinocyte overproduction of fatty acids and modification of lipid metabolism characterized by increased synthesis phospholipids, arachidonic acid metabolites and 12L-hydroxy 5,8,10,14-eicosatetraenoic acid have been hypothesized to cause the changes in skin pH.[19] Keratinocyte hyperproliferation in psoriasis further enhanced overproduction of these substances. We found significantly higher skin pH on the plaques in comparison to uninvolved skin. Delfino et. al.[20] and Maroto-Morales et. al.[5] reported no significant differences between the pH of plaques and uninvolved skin in psoriasis patients. The use of moisturizer may explain the higher pH seen among our patients. Majority of our patients used aqueous cream with pH of 7.32 - 7.58.[22] Application of aqueous cream on the plaques may cause the pH to be higher compared to the perilesional area where moisturizer was not applied. Cannovo et al.[16] reported lower skin pH at both plaques and perilesional areas compared to healthy controls. Similarly, another study showed lower pH at plaques and uninvolved skin in psoriasis patients compared to healthy controls.[5] Skin pH is influenced by various factors including age, gender, anatomical site and type of skin products

used. Some of these confounders may affect the results if skin pH is compared between different individuals versus comparison of measurements at different sites in the same individual.

Pruritus is commonly associated with psoriasis. Pruritus affects 64–98% of patients with psoriasis.[9-10,23-25] Pruritus can be a disabling symptom and a common cause of morbidity in psoriasis patients, which caused negative impact on their quality of life.[20-23] Factors associated with severe pruritus were female sex, body mass index >30kg/m^2, severe psoriasis and genital psoriasis.[10,18,20,26-27] We did not find significant associations between TEWL, SC hydration and skin pH with itch score. However, about a third of our patients did complain of pruritus. Contribution of abnormalities in skin barrier towards itch in psoriasis needs to be further investigated as to the best of our knowledge there is currently no other data on this topic.

Limitations

Our study involved patients with mild psoriasis only. The relationship between TEWL, stratum corneum hydration and skin pH with itch maybe better demonstrated with inclusion of patients with moderate and severe disease. The lack of healthy control is another limitation of this study. However, comparison with normal appearing skin within the same subject has the advantage of avoiding confounding factors like type of skin cleanser and moisturizer which may affect the results of the measured skin parameters.

Conclusion

There is a marked defective skin barrier function in chronic plaque psoriasis. Our study demonstrated increased TEWL, reduced sc hydration and increased pH even among patients with mild disease. There was no association between TEWL, SC hydration and skin surface pH with itch in patients with mild psoriasis. Understanding the skin biophysical properties in psoriasis is useful to explore possible aetiopathogenic mechanism for future therapeutic approaches.

Conflict of Interests Declaration

The authors declared no potential conflicts of interest with respect to research, authorship and/or publication of this article.

Acknowledgement

Special thanks to Encik Zamtira bin Seman, Clinical Research Centre, Institut Kesihatan Umum, Setia Alam, Shah Alam, Selangor for his assistance in statistical analyses. The authors received financial support from Universiti Kebangsaan Malaysia – SULAM@UKM for the research.

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ORIGINAL ARTICLE

Physician-perceived Barriers to Systemic and Biological Treatments In Moderate-to-severe Psoriasis in Malaysia

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Abstract

Background

Despite guideline recommendations and availability of systemic and biologic agents for moderate-to-severe psoriasis, many patients are still not receiving appropriate treatment. We aimed to identify physician-perceived barriers to the use of conventional systemic versus biologic treatments for psoriasis and investigate physician characteristics associated with the different types of barriers.

Methods

We conducted a survey involving 59 dermatologists practising in Malaysia where perceived barriers to treatments were assessed based on a 4-point Likert scale. Descriptive analysis was performed for baseline characteristics and treatment barriers. The McNemar's test was used to compare between the two treatment categories while the Pearson's chi-squared test (and Fisher's exact test where applicable) were used to identify associated physician factors.

Results

The presence of comorbidities (p=0.003), side effect of medications (p=0.049), frequency of monitoring and follow-up (p=0.013) and higher risk-benefit ratios (p=0.016) were identified as barriers to the use of conventional systemic treatment, as compared to biologic treatment, where the time and paperwork needed to initiate treatment (p=0.007), cost of medication (p=0.001) and difficulty in obtaining funding for public sector patients (p<0.001) were the barriers reported.

Conclusion

Although biologic drugs are perceived as safer than conventional systemic agents, financial concerns pose a major barrier to the use of these agents among Malaysian patients with psoriasis.

Key words: *Biologic drug, drug prescribing, prescribing patterns, psoriasis*

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Introduction

The use of systemic therapy or biologics is often recommended for patients with severe psoriasis and those with moderate psoriasis and impairment of quality of life. Data from the Malaysian Psoriasis Registry (MPR) showed that 23.9% of adult patients and 17.2% of paediatric patients had more than 10% of body

surface area (BSA) involvement.[1] Additionally, 13.8% of adult patients and 2.4% of paediatric patients had been diagnosed with psoriatic arthritis.[1] Despite these numbers, only 19.2% of adult patients and 8.8% of paediatric patients received systemic therapy.[1] The use of biologics was even lower with only 1.1% of adult patients and 0.3% of paediatric patients prescribed with these drugs.[1] Consequently, psoriasis may be under-treated with patients unable to achieve treatment goals both in terms of reduction in BSA involvement and improvement in Dermatology Life Quality Index (DLQI). With the availability of modern and effective treatment options, these findings demonstrate a pressing need to evaluate the possible reasons patients are not able to access systemic and/or biologic drugs even if indicated based on our national treatment guidelines.

This scenario has also been reported in other countries such as in Canada where 82% of patients with moderate-to-severe psoriasis had never received phototherapy and/or systemic therapy despite more than 50% of them indicating willingness to consider systemic therapy.[2] In the United Kingdom, only 4% of patients received phototherapy or systemic therapy between 2002 to 2003, whereas 93.6% of patients received purely topical treatment.[3] Similarly, a study conducted in 2006 in Germany found that systemic drugs were prescribed for 31% of patient visits for moderate-to-severe psoriasis whereas only 2% received biologics.[4] In Southern Philippines, the most prescribed systemic drug was methotrexate (24.4%) followed by acitretin (3.8%) and cyclosporine (0.8%) while only 6.1% of patients were treated with biologics.[5] Data from a statutory health insurance company in Germany between 2004 to 2007 showed that 11% of patients with psoriasis were treated with systemic drugs while only 0.1% were treated with biologics.[6]

As the data clearly shows a gap in the treatment of moderate-to-severe psoriasis in Malaysia, we aimed to identify physician-perceived barriers to the use of systemic and biological treatments for psoriasis in our local setting. We also assessed physician characteristics in terms of gender, experience in terms of number of years working as a dermatologist and types of practice settings which were associated with the different barrier categories.

Materials and Methods

A cross-sectional anonymous survey was conducted among dermatologists in Malaysia to identify perceived barriers to the use of systemic and biological treatments in managing patients with moderate to severe psoriasis (more than 10% body surface area involvement).[1] Common systemic treatments used in Malaysia include methotrexate, acitretin and cyclosporin while common biological treatments used include secukinumab, ixekizumab, guselkumab, ustekinumab and others. Barriers for two treatment categories namely conventional systemic therapy and biological treatments were assessed on a 4-point Likert scale ("Not a barrier", "Mild barrier", "Moderate barrier", "Strong barrier"). Items in the survey were based on possible barriers identified in a literature review by the authors. To facilitate statistical analysis, scoring for each individual item was divided into "barrier" (moderate or strong barrier) or "not a barrier" (no barrier or mild barrier). Data on demographics, type of practice setting (government or academic institution versus private), years of experience and percentage of moderate-to-severe psoriasis seen in their dermatology practices were collected. Survey forms (appendix 1) and informed consent forms in the English language were distributed electronically via e-mail to registered members of the Dermatological Society of Malaysia as well as during an in-person meeting of the society using convenience sampling. This survey was carried out within 3 months' period from August until October 2022. The study received ethical approval from National Medical Research Register Malaysia (NMRR ID-22-01313-RED).

Descriptive analysis was performed for demographics, baseline characteristics and prevalence of treatment barriers assessed in

the survey. The McNemar's test was used to compare between common possible barriers for biological treatments versus systemic treatments. The Pearson's chi-squared test (and Fisher's exact test where applicable) were used to identify physician factors associated with perceived barriers. All tests were two-tailed with *p*-value of less than 0.05 defined as statistically significant.

Results

A total of 59 dermatologists responded to the invitation to participate in the survey, leading to a response rate of 46.1% (n=59/128). The male to female ratio was 0.64 with a median age of 44 years (interquartile range, IQR=41, 48) (Table 1). The median number of years of experience as a dermatologist was 7 years (IQR=2.5, 12) with 27.1% (n=16) recording more than ten years of experience while 23.7% (n=14) recording of two or less years of experience. Most of the respondents worked in government healthcare facilities or academic institutions (72.9%, n=43) while 16 dermatologists (27.1%) worked in the private sector. A median of 30% (IQR=15, 50) of patients seen in their practices for psoriasis had moderate to severe disease.

Physician-related concerns

Time and paperwork prior to commencing biologic therapy were more likely to pose a barrier to use compared to systemic therapy (*p*=0.007) (Table 2). Conversely, patient comorbidities were more likely to be barriers for conventional systemics rather than for biologic agents (*p*=0.003). For both conventional systemic and biologic therapy, most respondents felt that experience and knowledge were not barriers to initiate these medications. They were also confident in the recommendations in the treatment guidelines for both systemic and biologic therapy. Investigations prior to starting treatment, monitoring of patients on treatment and availability of support staff were not reported to be moderate/strong barriers for either type of treatment.

Table 1. Demographics of 59 dermatologists who participated in this survey

Characteristics	Median (IQR)
Age (Years)	44 (41,48)
Number of years working as dermatologist (Years)	7 (2.5, 12)
Percentages of patients with moderate-severe psoriasis (%)	30 (15, 50)
Characteristics	**N (%)**
Gender	
- Female	36 (61.0%)
- Male	23 (39.0%)
Type of practice	
- Government with some private practice	22 (37.3%)
- Government only (Ministry of Health)	17 (28.8%)
- Private Only	16 (27.1%)
- University with some private practice	3 (5.1%)
- University Only	1 (1.%)
Years of working experience as dermatologist	
- 0 – 2 years	14 (23.7%)
- 3 – 10 years	29 (49.2%)
- More than 10 years	16 (27.1%)

Patient-related concerns

The dermatologists reported that patients were more likely to be concerned about potential side effects for systemics rather than biologics (52.6% versus 35.6%, *p*=0.049) while there was no significant difference between the two categories of treatment in terms of concerns about efficacy (Table 2). Majority of respondents (62.7%) reported that out-of-pocket costs were a strong barrier for biologic treatment compared to 44.1% reporting likewise for systemics. However, when analysed in terms of either posing a barrier (moderate/strong) or not, there was no statistical difference between the two categories (*p*=0.052).

Difficulty adhering to monitoring and attending follow-up visits were important patient-related concerns that pose as barriers to treatment when given systemics (37.3%) compared to biologics (20.4%) (*p*=0.013). Interestingly, difficulty adhering to treatment regimens was neither a barrier for systemics nor biologics and fear of needles or preference for oral medications was not a barrier/mild barrier to the use of biologics (77.9%).

Table 2. Factors which represent a barrier to use of systemic and biologic treatments for moderate-severe psoriasis

	Systemic therapy					Biologic therapy					*p*-value*
Barriers to treatments for moderate-severe psoriasis	Not a barrier n (%)	Mild barrier n (%)	Moderate barrier n (%)	Strong barrier n (%)	No response n (%)	Not a barrier n (%)	Mild barrier n (%)	Moderate barrier n (%)	Strong barrier n (%)	No response n (%)	
Physician concerns											
1. My experience in the use of systemic treatments	46 (78.0)	10 (16.9)	3 (5.1)	-	-	31 (52.5)	20 (33.9)	6 (10.2)	1 (1.7)	1 (1.7)	0.219
2. My knowledge in the use of systemic treatments	49 (83.1)	9 (15.3)	1 (1.7)	-	-	36 (61.0)	18 (30.5)	4 (6.8)	-	1 (1.7)	0.375
3. My confidence in the treatment guidelines	48 (81.4)	10 (16.9)	1 (1.7)	-	-	36 (61.0)	18 (30.5)	3 (5.1)	-	1 (1.7)	0.625
4. Time and paperwork needed to start a patient on systemic treatments	36 (61.0)	17 (28.8)	6 (10.2)	-	-	18 (30.5)	23 (39.0)	14 (23.7)	3 (5.1)	1 (1.7)	0.007
5. Investigations prior to starting systemic treatment	33 (55.9)	19 (32.2)	7 (11.9)	-	-	24 (40.7)	27 (45.8)	5 (8.5)	2 (3.4%	1 (1.7)	1.000
6. Monitoring for a patient on systemic treatment	34 (57.6)	19 (32.2)	6 (10.2)	-	-	31 (52.5)	22 (37.3)	3 (5.1)	2 (3.4)	1 (1.7)	1.000
7. My colleagues' views and opinions on a particular systemic drug	43 (72.9)	11 (18.6)	3 (5.1)	-	2 (3.4)	44 (74.6)	12 (20.3)	2 (3.4)	1 (1.7)	-	1.000
8. Patient's comorbidities	17 (28.8)	18 (30.5)	20 (33.9)	3 (5.1)	1 (1.7)	19 (32.2)	27 (45.8)	11 (18.6)	1 (1.7)	1 (1.7)	0.003
9. Insufficient support staff	35 (59.3)	19 (32.2)	4 (6.8)	-	1 (1.7)	30 (50.8)	21 (35.6)	7 (11.9)	-	1 (1.7)	0.375
	Systemic therapy					**Biologic therapy**					***p*-value***
Barriers to treatments for moderate-severe psoriasis	Not a barrier n (%)	Mild barrier n (%)	Moderate barrier n (%)	Strong barrier n (%)	No response n (%)	Not a barrier n (%)	Mild barrier n (%)	Moderate barrier n (%)	Strong barrier n (%)	No response n (%)	
Patient concerns											
1. Patient's concern regarding efficacy of treatment.	11 (18.6)	33 (55.9)	14 (23.7)	1 (1.7)	-	18 (30.5)	29 (49.2)	11 (18.6)	-	1 (1.7)	0.289
2. Patients' concern regarding potential side effects	5 (8.5)	23 (39)	28 (47.5)	3 (5.1)	-	9 (15.3)	28 (47.5)	21 (35.6)	-	1 (1.7)	0.049
3. Patients' concern regarding out-of-pocket cost	10 (16.9)	14 (23.7)	9 (15.3)	26 (44.1)	-	2 (3.4)	12 (20.3)	7 (11.9)	37 (62.7)	1 (1.7)	0.052
4. Difficulty adhering to monitoring and attending follow up visits	4 (6.8)	33 (55.9)	21 (35.6)	1 (1.7)	-	15 (25.4)	31 (52.5)	9 (15.3)	3 (5.1)	1 (1.7)	0.013
5. Difficulty adhering to treatment regimens	8 (13.6)	35 (59.3)	16 (27.1)	-	-	18 (30.5)	30 (50.8)	9 (15.3)	1 (1.7)	1 (1.7)	0.146
6. Fear of needles or preference of oral treatment	-	-	-	-	-	14 (23.7)	32 (54.2)	9 (15.3)	3 (5.1)	1 (1.7)	-

Barriers to treatments for moderate-severe psoriasis	Systemic therapy					Biologic therapy					*p*-value*
	Not a barrier n (%)	Mild barrier n (%)	Moderate barrier n (%)	Strong barrier n (%)	No response n (%)	Not a barrier n (%)	Mild barrier n (%)	Moderate barrier n (%)	Strong barrier n (%)	No response n (%)	
External factors											
1. Cost of treatment is too expensive	8 (13.6)	13 (22.0)	10 (16.9)	28 (47.5)	-	1 (1.7)	4 (6.8)	7 (11.9)	47 (79.7)	-	0.001
2. Difficulty obtaining funding (for government/ university patients)	12 (20.3)	13 (22.0)	7 (11.9)	22 (37.3)	5 (8.5)	4 (6.8)	3 (5.1)	7 (11.9)	40 (67.8)	5 (8.5)	0.000
3. Difficulty obtaining a supply	29 (49.2)	15 (25.4)	11 (18.6)	4 (6.8)	-	23 (39.0)	17 (28.8)	6 (10.2)	13 (22.0)	-	0.388
4. Obligatory step therapy as per guideline recommendations	-	-	-	-	-	13 (22.0)	23 (39.0)	14 (23.7)	9 (15.3)	-	-
	Systemic therapy					**Biologic therapy**					***p*-value***
Barriers to treatments for moderate-severe psoriasis	Not a barrier n (%)	Mild barrier n (%)	Moderate barrier n (%)	Strong barrier n (%)	No response n (%)	Not a barrier n (%)	Mild barrier n (%)	Moderate barrier n (%)	Strong barrier n (%)	No response n (%)	
Concerns regarding the drug themselves											
1. I have doubts regarding the efficacy of systemic treatment	39 (66.1)	16 (27.1)	4 (6.8)	-	-	47 (79.7)	12 (20.3)	-	-	-	0.125
2. I have doubts regarding the safety of systemic treatment	35 (59.3)	17 (28.8)	7 (11.9)	-	-	42 (71.2)	15 (25.4)	2 (3.4)	-	-	0.063
3. The risk-benefit ratio is not adequate	31 (52.5)	20 (33.9)	7 (11.9)	1 (1.7)	-	44 (74.6)	14 (23.7)	1 (1.7)	-	-	0.016
4. There is insufficient scientific evidence on treatment	39 (66.1)	16 (27.1)	2 (3.4)	2 (3.4)	-	44 (74.6)	13 (22.0)	1 (1.7)	1 (1.7)	-	0.625
5. Topical treatment and/or phototherapy are enough for most patients	26 (44.1)	21 (35.6)	7 (11.9)	5 (8.5)	-	29 (49.2)	17 (28.8)	10 (16.9)	3 (5.1)	-	1.000

**McNemar test*

External factors

The proportion of respondents who found that the cost of biological drugs was too expensive was significantly higher compared to conventional systemic treatment (91.6% versus 64.4%, p=0.001) (Table 2). Subsequently, government and university hospital patients had greater difficulty obtaining funding for biologics compared to systemic drugs (79.7% versus 49.2%, p<0.001). Difficulty in obtaining supply of medication was a barrier to treatment in only 25.4% for systemics and 32.2% for biologics (p=0.388). On the other hand, less than half the respondents felt that obligatory step therapy was a barrier to treatment with biologics (23.7% for moderate barrier and 15.3% for strong barrier).

Concerns regarding the drug themselves

Inadequate risk-benefit ratio was a barrier to treatment for 13.6% of respondents intending to use systemics while only one respondent felt that this situation was a moderate barrier to biologics use (1.7%) (p=0.016) (Table 2).

Most respondents did not consider doubts regarding either the efficacy or safety of both systemic (93.2% and 88.1% respectively) and biologic treatments (100.0% and 96.6% respectively) as barriers to therapy. Furthermore, only 6.8% and 3.4% of respondents felt that

insufficient scientific evidence was a moderate/strong barrier to treatment with conventional systemics and biologic agents respectively. Majority of the respondents also reported that the adequacy of topical treatment and/or phototherapy was either not a barrier or only posed a mild barrier for treatment with systemics and biologic agents respectively (79.7% and 78.0%).

Physician characteristics associated with barrier in initiating systemic treatment

For systemic treatments, respondents who worked only in the private sector were more likely to find that pre-initiation investigations (p=0.001) and monitoring during treatment (p=0.004) were barriers to initiating treatment (Table 3). Furthermore, the respondents reported that patients attending private dermatology clinics were more likely to have concerns regarding efficacy of treatment (p=0.016) as well as out-of-pocket costs (p=0.001) which were hence perceived as barriers to initiation of systemic treatment (Table 4). In terms of patient concerns regarding potential side effects, dermatologists with more than ten years of experience were more likely to regard this issue as a barrier to initiating systemic treatment (p=0.035).

In terms of concerns about systemic drugs, respondents in the private sector were more likely to report that doubts regarding safety (p=0.013) and inadequate risk-benefit ratio (p=0.028) were barriers to treatment initiation (Table 5). Respondents with more than 10 years of experience were also more likely to find that inadequate risk-benefit ratio was a barrier to systemic treatment (p=0.028).

Physician characteristics associated with barrier in initiating biologic treatment

Respondents who worked only in the private sector were more likely to find that their confidence in treatment guidelines (p=0.019) and investigations prior to starting biologic treatments (p=0.014) were moderate-to-strong barriers to initiating biologic treatment for psoriasis (Table 3).

Table 3. Factors associated with physician-related concerns which pose a barrier to the initiation of systemic or biologic therapies

(A) Systemic therapy									
	My experience in the use of systemic treatments, OR (95% CI)	My knowledge in the use of systemic treatments, OR (95% CI)	My confidence in the treatment guidelines, OR (95% CI)	Time and paperwork needed to start a patient on systemic treatments, OR (95% CI)	Investigations prior to starting systemic treatment, OR (95% CI)	Monitoring for a patient on systemic treatment, OR (95% CI)	My colleagues' views and opinions on a particular systemic drug, OR (95% CI)	Patient's comorbidities, OR (95% CI)	Insufficient support staff, OR (95% CI)
More than 10 years of experience	1.367* (0.115-16.194)	1.024* (0.978-1.072)	1.024* (0.978-1.072)	1.393* (0.229-8.459)	2.250* (0.444-11.406)	1.393* (0.229-8.459)	1.429* (0.120-16.998)	2.133# (0.647-7.031)	3.154* (0.403-24.667)
Government sector	0.167* (0.014-1.981)	N.A.*	N.A. *	1.974*(0.213-18.330)	**0.040* (0.004-0.368)**	**0.052* (0.006-0.496)**	0.159* (0.014-1.894)	0.469# (0.142-1.545)	0.095* (0.009-1.001)
(B) Biologic therapy									
	My experience in the use of biologic treatments, OR (95% CI)	My knowledge in the use of biologic treatments, OR (95% CI)	My confidence in the treatment guidelines, OR (95% CI)	Time and paperwork needed to start a patient on biologic treatments, OR (95% CI)	Investigations prior to starting biologic treatment, OR (95% CI)	Monitoring for a patient on biologic treatment, OR (95% CI)	My colleagues' views and opinions on a particular biologic drug, OR (95% CI)	Patient's comorbidities, OR (95% CI)	Insufficient support staff, OR (95% CI)
More than 10 years of experience	1.169 (0.202-6.773)	0.952 (0.091-9.922)	1.429 (0.120-16.998)	0.518 (0.126-2.136)	4.848 (0.942-24.968)	2.051 (0.308-13.652)	3.000 (0.176-51.195)	1.591 (0.401-6.313)	2.438 (0.447-12.451)
Government sector	0.231 (0.045-1.179)	0.106 (0.010-1.106)	**N.A.**	1.345 (0.364-4.970)	**0.110 (0.019-0.646)**	0.217 (0.033-1.442)	N.A.	0.440 (0.116-1.668)	0.456 (0.090-2.314)

OR: Odds Ratio; CI: Confidence Interval; N.A.: Not Applicable

*#Chi-square; *Fisher's exact test*

Table 4. Physician characteristics associated with patient-related concerns which pose a barrier to the initiation of systemic or biologic therapies

	Patient's concern regarding efficacy of treatment, OR (95% CI)	Patients' concern regarding potential side effects, OR (95% CI)	Patients' concern regarding out-of-pocket cost, OR (95% CI)	Difficulty adhering to monitoring and attending follow up visits, OR (95% CI)	Difficulty adhering to treatment regimens, OR (95% CI)	Fear of needles or preference of oral treatment, OR (95% CI)
(A) Systemic therapy						
More than 10 years of experience	2.267* (0.649-7.917)	**3.789# (1.052-13.652)**	2.609# (0.725-9.387)	1.013# (0.309-3.315)	0.861* (0.232-3.202)	
Government sector	**0.194* (0.055-0.693)**	0.395# (0.117-1.332)	**0.058# (0.007-0.479)**	0.483# (0.150-1.554)	0.505* (0.147-1.736)	
(B) Biologic therapy						
More than 10 years of experience	1.870* (0.460-7.598)	2.637# (0.790-8.802)	1.375* (0.326-5.796)	0.944* (0.219-4.079)	0.270* (0.031-2.334)	0.508* (0.098-2.639)
Government sector	0.367* (0.094-1.436)	0.311# (0.094-1.026)	1.067* (0.280-4.057)	0.278* (0.073-1.051)	0.297* (0.073-1.218)	1.182* (0.276-5.067)

OR: Odds Ratio; CI: Confidence Interval; N.A.: Not Applicable
*#Chi-square; *Fisher's exact test*

Table 5. Physician characteristics associated with concerns regarding the drugs themselves which pose a barrier to the initiation of systemic or biologic therapies

(A) **Systemic therapy**					
	I have doubts regarding the efficacy of systemic treatment, OR (95% CI)	I have doubts regarding the safety of systemic treatment, OR (95% CI)	The risk-benefit ratio is not adequate, OR (95% CI)	There is insufficient scientific evidence on treatment, OR (95% CI)	Topical treatment and/or phototherapy are enough for most patients, OR (95% CI)
More than 10 years of experience	0.889* (0.086-9.225)	4.444* (0.871-22.685)	**6.061* (1.249-29.402)**	0.889* (0.086-9.225)	2.338 (0.617-8.852)
Government sector	0.103* (0.010-1.079)	**0.107* (0.018-0.630)**	**0.165* (0.034-0.800)**	0.341* (0.044-2.657)	0.686* (0.175-2.692)
(B) **Biologic therapy**					
	I have doubts regarding the efficacy of biologic treatment	I have doubts regarding the safety of biologic treatment	The risk-benefit ratio is not adequate	There is insufficient scientific evidence on treatment	Topical treatment, phototherapy and/or conventional systemic drugs are enough for most patients
More than 10 years of experience	NA	2.80* (0.165-47.628)	1.024* (0.978-1.072)	NA	1.989* (0.528-7.346)
Government sector	NA	NA	NA	NA	2.406* (0.470-12.309)

OR: Odds Ratio; CI: Confidence Interval; NA: Not Applicable
*#Chi-square; *Fisher's exact test*

Discussion

Eissing et al. classified barriers to guideline-compliant psoriasis care into three categories, namely: patient factors, physician factors and external factors.[7] From the patient's perspective, barriers included limited knowledge about treatment options, definition of treatment modalities without taking into account patients' views, psychological issues and economic limitations. Barriers due to physician factors were a lack of knowledge (regarding treatment guidelines, goals of therapy and assessment methods), recommendations for step therapy in guidelines, financial concerns and comorbidities associated with psoriasis. Lastly, external barriers included limited health care infrastructure, lack of incentives for setting treatment goals and a wide variability in terms of assessment tools.[7]

In an international survey, Nast et al. reported that safety concerns and the risk-benefit ratio

were barriers to the use of conventional systemic therapies for moderate-to-severe psoriasis while economic considerations were more commonly cited barriers to the prescription of biological drugs.[8] Physician characteristics were determinants of treatment barriers, particularly in terms of type of practice setting and nationality.

Similarly, we found that most of the barriers to the use of systemic treatment were related to the safety profile of the drugs as well as patient comorbidity profile, while the main barriers to the use of biologic drugs were due to economic concerns. The annual cost of biologics in the United States ranges from USD 38,538 to USD 65,484.[9] In Brazil, the mean annual cost for a patient with moderate-to-severe psoriasis was USD 4034 with 87.7% attributed to direct medical costs, indirect costs 9.9% and direct non-medical costs 2.4%.[10] In a study conducted in Finland, only 5% of psoriasis patients required biologics but these drugs accounted for 67% of the medication costs.[11] A survey among patients with psoriasis in China found that the most important factor in terms of preference for biologics was the cost of treatment.[12]

Among patients with psoriasis, those treated on biologics incur the highest all-cause healthcare costs, mostly attributed to outpatient pharmacy costs.[13] On the other hand, a Korean study reported that self-funded patients were more likely to discontinue ustekinumab compared to insurance-funded patients.[14] This illustrates the importance of improving access to biologic treatment for patients with psoriasis, particularly for those in the lower income brackets as these drugs have proven efficacy and safety for moderate-to-severe psoriasis. Patient support programmes as well as optimising the cost of medications may be useful steps to achieve this aim.

Another cost-effective approach would be to consider biosimilar drugs as a first-line biological treatment option for moderate-to-severe psoriasis, particularly in a public healthcare setting.[15] Although biological drugs may be expensive, the increased cost can be offset by better efficacy, reduced disease burden, high patient satisfaction, better work productivity and lower health care resource utilization including reduced hospitalisation.[16-21] From a patient's perspective, financial considerations (particularly for government-funded patients) may make it difficult for them to access biological treatments and lead to a fear of discontinuation after disease improvement.[22] The high cost of treatment may also lead to poor adherence.[23]

A questionnaire-based study in Bavaria found that the main barriers to the use of biologics for psoriasis and chronic spontaneous urticaria were financial concerns, low reimbursement and fear of recourse. The factors associated with the perception of barriers were the clinical education and experience of the physicians where those with more experience tended to place more emphasis on patient concerns.[24] However, in our study, longer duration of experience was associated with the perception that patient concerns regarding side effects were barriers for systemic treatment but not for biologic treatment.

In terms of barriers to the use of conventional systemics, dermatologists in the private sector reported more concerns regarding pre-initiation investigations, efficacy, safety, risk-benefit ratio, monitoring and out-of-pocket costs. For biologics, private dermatologists were more likely to express concerns regarding confidence in treatment guidelines and the need for pre-initiation investigations posing as barriers to initiation of treatment. Conversely private dermatologists in Germany mostly found that the German Psoriasis Guidelines were useful with 80% reporting that they had amended treatment decisions based on these guidelines.[25]

In Malaysia, Azizam et al conducted a cost-effectiveness study of psoriasis treatments especially for the moderate-to-severe psoriasis patients in 2016 which compared three arms of interventions, namely topical and phototherapy (TP), topical and systemic treatments (TS) and topical and biologic treatments (TB).[26] TB regimen had proven to show the highest

effectiveness while TS treatment was considered the most cost-effective strategy taking into account all the direct and indirect costs associated with the treatment of moderate-severe psoriasis. This should guide clinicians and policy makers in deciding the best first line treatment for patients with moderate to severe psoriasis in Malaysia.

There are currently a few options of financial supports for patients with severe psoriasis requiring biological therapy when systemic treatments have failed or are unsuitable in Malaysia. Patients who are federal pensioners, civil servants or their dependants (husband or wife) and children under 18 years old, may apply for funding from the Public Service Department where financial support can be considered on a case-by-case basis.[27] For patients who are not civil servants or dependents, they can apply for funding via "*Tabung Bantuan Perubatan*" and this will also be considered on a case-by-case basis.[28] Other funding options include non-governmental organisations, charities or religious bodies. For these funding applications, physicians are burdened with laborious paperwork. The time frame needed for approval of these applications range between one to six months. Once the application for biologics is approved, this is usually given for six months to a year after which a fresh application will need to be resubmitted. For private patients, they would either depend on insurance funding or pay out-of-pocket for their treatment.

The limitation of our study was the response rate to our survey which was slightly less than half the total number of dermatologists invited to participate and this could have resulted in selection bias.

Conclusion

Patients with moderate to severe psoriasis require systemic or biological therapies. Although biological therapies were proven to be more effective while systemic treatments were proven to be more cost-effective in a previous study, financial concerns remain as a major barrier for physicians to initiation of these important treatments for our patients. We hope policy makers are aware of these physician-perceived barriers and take necessary steps to provide essential financial supports to patients with moderate to severe psoriasis in Malaysia.

Conflict of Interest Declaration

All authors have no financial/conflict of interest to be disclosed.

Acknowledgement

We would like to acknowledge all dermatologists in Malaysia who had participated in this questionnaire survey.

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Appendix 1: Questionnaire Survey:

Dear Datuk/Dato/Prof/Dr,

As you are aware, the Malaysian Psoriasis Registry is involved in collecting and analysing data regarding the characteristics and treatment of patients with psoriasis in our country. We would like to invite you to participate in a survey to evaluate the barriers to the use of systemic and biological treatments for psoriasis. This survey will be confidential and will take approximately 15 minutes for you to complete.

There are 3 separate sections in this survey:
(A) Physician characteristics
(B) Barriers to systemic treatment
(C) Barriers to biological treatment

We thank you in advance for your kind cooperation and support.

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(A) Physician characteristics

Gender: □ Male □ Female

Age: [ ]

Years worked as a dermatologist: [ ]

Type of practice:
□ Government only (Ministry of Health)
□ University only
□ Private only
□ Government with some private practice
□ University with some private practice
□ Others: [ ]

Among your psoriasis patients, what is the percentage of patients seen with moderate-to-severe disease? [ ]

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(B) Systemic treatment

For the following statements, please provide a rating as to how much these factors represent a barrier to the use of conventional systemic treatment for psoriasis:
1-Not a barrier
2-Mild barrier
3-Moderate barrier
4-Strong barrier

Physician concerns:

	1	2	3	4
1. My experience in the use of systemic treatments				
2. My knowledge in the use of systemic treatments				
3. My confidence in the treatment guidelines				
4. Time and paperwork needed to start a patient on systemic treatments				
5. Investigations prior to starting systemic treatment				
6. Monitoring for a patient on systemic treatment				
7. My colleagues' views and opinions on a particular systemic drug				
8. Patients' comorbidities				
9. Insufficient support staff				

Patient concerns:

	1	2	3	4
1. Patient concerns regarding efficacy of treatment				
2. Patient concerns regarding potential side effects				
3. Patient concerns regarding out-of-pocket costs				
4. Difficulty adhering to monitoring and attending follow-up visits				
5. Difficulty adhering to treatment regime				

External factors:

	1	2	3	4
1. Cost of treatment is too expensive				
2. Difficulty obtaining funding (for government/university patients)				
3. Difficulty obtaining supply of drug				

Concerns regarding the drugs themselves:

	1	2	3	4
1. I have doubts regarding the efficacy of systemic treatment				
2. I have doubts regarding the safety of systemic treatment				
3. The risk-benefit ratio is not adequate				
4. There is insufficient scientific evidence on the treatment				
5. Topical treatment and/or phototherapy are enough for most patients				

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(C) Biological treatment

For the following statements, please provide a rating as to how much these factors represent a barrier to the use of biological treatment for psoriasis:
1-Not a barrier
2-Mild barrier
3-Moderate barrier
4-Strong barrier

Physician concerns:

	1	2	3	4
1. My experience in the use of biologic therapy				
2. My knowledge in the use of biologic therapy				
3. My confidence in the use of biologic therapy				
4. Time and paperwork needed to start a patient on biologic therapy				
5. Investigations prior to starting biologic therapy				
6. Monitoring for a patient on biologic therapy				
7. My colleagues' views and opinions on biologics				
8. Patients' comorbidities				
9. Insufficient support staffs				

Patient concerns:

	1	2	3	4
1. Patient concerns regarding efficacy of treatment				
2. Patient concerns regarding potential side effects				
3. Patient concerns regarding out-of-pocket costs				
4. Difficulty adhering to monitoring and attending follow-up visits				
5. Difficulty adhering to treatment regime				
6. Fear of needles or preference for oral treatment				

External factors:

	1	2	3	4
1. Cost of treatment is too expensive				
2. Difficulty obtaining funding (for government/university patients)				
3. Difficulty obtaining supply of drug				
4. Obligatory step therapy as per guideline recommendations				

Concerns regarding the drugs themselves:

	1	2	3	4
1. I have doubts regarding the efficacy of biologic therapy				
2. I have doubts regarding the safety of biologic therapy				
3. The risk-benefit ratio is not adequate.				
4. There is insufficient scientific evidence of biologic therapy				
5. Topical treatment, phototherapy and/or conventional systemic drugs are enough for most patients				

Thank you for your participation!

ACKNOWLEDGEMENT
Dec Issue 2023

The Editorial Board of The Malaysian Journal of Dermatology gratefully acknowledge the following individuals for reviewing the papers submitted for publication:

1. Assoc Professor Dr Adawiyah Jamil
2. Dr Ch'ng Chin Chwen
3. Dr Chang Choong Chor
4. Dr Henry Foong Boon Bee
5. Dr Irene Lee Chew Kek
6. Dr Kwan Zhenli
7. Dr Michelle Voo Sook Yee
8. Dr Ng Ting Guan
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11. Dr Sharifah Rosniza Syed Nong Chek
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