Causes of mortality in patients with psoriasis in Malaysia – Evidence from the Malaysian Psoriasis Registry

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ABSTRACT

Background: Patients with severe psoriasis, namely those requiring phototherapy or systemic treatment, have an increased risk of death. The aim of this study was to determine the prevalence, aetiology and risk factors for mortality among adult patients aged 18 years and above with psoriasis in Malaysia.

Methods: This was a retrospective study involving adult patients notified by dermatologists to the Malaysian Psoriasis Registry between July 2007 and December 2013. Data were cross-checked against the National Death Registry. Patients certified dead were identified and the cause of death was analysed. Multivariate analysis using multiple logistic regression were conducted on potential factors associated with higher risk of mortality.

Results: A total of 419 deaths were identified among the 9775 patients notified. There were four significant risk factors for higher mortality: age>40 years (age 41-60 years old, Odds Ratio (OR) 2.70, 95%CI 1.75, 4.18; age>60 years OR 7.46, 95%CI 4.62, 12.02), male gender (OR 1.72, 95%CI 1.33,2.22), severe psoriasis with body surface area (BSA) >10% (OR 1.52, 95%CI 1.19, 1.96) and presence of at least one cardiovascular co-morbidity (OR 1.67, 95% CI 1.30, 2.14). Among the 301 patients with verifiable causes of death, the leading causes were infection (33.9%), cardiovascular disease (33.6%) and malignancy (15.9%).

Conclusion: Infection was the leading cause of death among psoriasis patients in Malaysia. Although cardiovascular diseases are well-known to cause significant morbidity and mortality among psoriasis patients, the role of infections and malignancy should not be overlooked.

KEY WORDS:
Psoriasis, epidemiology, mortality

INTRODUCTION

Psoriasis is a common chronic dermatologic condition affecting approximately 1.5-3.0% of the population. In the United States, 1.5% of hospitalised patients admitted for psoriasis died and based on nationwide death certificates, a mean of 0.64 deaths/100,000 patients a year was calculated.[1] In a Swedish study, patients with psoriasis also displayed an excessive overall mortality.[2] Patients with severe psoriasis have an increased risk of cardiovascular mortality that is independent of traditional cardiovascular risk factors,[3-6] as well as a higher risk of death due to other factors such as malignancies, chronic lower respiratory tract disease, diabetes mellitus, dementia, infections and kidney disease.[3] In this paper, we explore the prevalence, aetiology and risk factors for mortality among adult patients with psoriasis in Malaysia.

MATERIALS AND METHODS

This is a retrospective study involving adult patients aged 18 years and over notified to the Malaysian Psoriasis Registry between July 2007 and December 2013. This registry is a centralised electronic database, where data is collected voluntarily from 22 participating centres nationwide. The list of patients obtained was cross-checked against the National Death Registry and the various causes of death among the deceased patients were analysed.

Statistical analysis was performed using SPSS version 20. Simple logistic regression was performed to determine the role of cardiovascular risk factors affecting mortality while multivariate analysis using multiple logistic regression was performed to determine possible predictive factors of mortality such as age, age of onset (whether above the age of 40 years or not), gender, Body Surface Area (BSA) involvement, the use of systemic therapy and the presence of co-morbidities. Missing data were not included in the analysis. Enter method was applied. Multicollinearity was checked to ensure the correlation between predictive factors was not found. Pearson Chi-squared test was used to determine whether the use of systemic therapy was associated with infections, malignancies and cardiovascular diseases causing death as well as whether the severity of disease was associated with cardiovascular causes of mortality.

RESULTS

A total of 9775 patients were notified to the registry between July 2007 and December 2013, of which 419 deaths (4.3% of patients in the registry) were identified (313 males, 106 females). The mean age at demise was 60.2 ± 13.4 years.

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Table I: Cardiovascular risk factors in patients with psoriasis

Variables	Patient alive (n=9356)		Patient died (n=419)		Logistic Regression		
	n	(%)	n	(%)	Crude OR	(95% CI)	P-value[a]
Hypertension	2103	22.5	179	42.7	2.59	(2.12, 3.17)	<0.001
Diabetes Mellitus	1406	15.0	150	35.8	3.14	(2.55, 3.87)	<0.001
Dyslipidaemia	1406	15.0	108	25.8	1.97	(1.57, 2.47)	<0.001
Ischaemic heart disease	426	4.6	67	16.0	3.98	(3.01, 5.25)	<0.001
Cerebrovascular disease	107	1.1	25	6.0	5.47	(3.50, 8.56)	<0.001

*Result was based on available information. Percentage (%) was calculated based on number of cases over total number for each group (alive or dead).
[a] Wald statistic.

Table II: Predictive factors of higher mortality in patients with psoriasis

Variables	Patient alive (n=9356)		Patient died (n=419)		Multiple Logistic Regression[a]		
	n	(%)	n	(%)	Adj. OR	(95% CI)	P-value
1. Age:							
18-40 years	3538	37.8	46	11.0	1.00	-	-
41-60 years	3621	38.7	168	40.1	2.70	(1.75, 4.18)	<0.001
>60 years	1349	14.4	205	48.9	7.46	(4.62, 12.02)	<0.001
Missing	848	9.1	0	0.0	-	-	-
2. Age of onset:							
≤ 40 years (Type 1)	6317	67.5	145	34.6	1.00	-	-
> 40 years (Type 2)	2856	30.5	268	64.0	1.32	(1.00, 1.75)	0.049
Missing	183	2.0	6	1.4	-	-	-
3. Gender:							
Male	5162	55.2	313	74.7	1.72	(1.33, 2.22)	<0.001
Female	4194	44.8	106	25.3	1.00	-	-
4. BSA involved							
≤ 10%	5118	54.7	234	55.8	1.00	-	-
> 10%	1696	18.1	103	24.6	1.52	(1.19, 1.96)	0.001
Missing	2542	27.2	82	19.6	-	-	-
5. Systemic therapy							
Yes	1698	18.1	102	24.3			NS
No	7375	78.8	311	74.2			
Missing	283	3.0	6	1.4			
6. Co-morbidity:							
At least one	2905	31.0	251	59.9	1.67	(1.30, 2.14)	<0.001
None	6330	67.7	163	38.9	1.00	-	-
Missing	121	1.3	5	1.2	-	-	-

*Result was based on available information
Adj. OR = Adjusted odds ratio
[a] Enter method was applied
Multicollinearity was checked and not found
Hosmer-Lemeshow test (p=0.845), classification table (overall correctly classified percentage=94.8%) and area under the ROC curve (76.7%) were applied to check the model fitness

Table III: Reported causes of mortality among patients with psoriasis

Cause of mortality	Number of patients, n (%)
Infection	102 (33.9%)
Cardiovascular	101 (33.6%)
Malignancy	48 (15.9%)
Trauma	20 (6.6%)
Gastrointestinal	18 (6.0%)
Renal	6 (2.0%)
Lung	6 (2.0%)
Total	301 (100.0%)

Table IV: Types of infections and malignancy-related deaths

Types	Number, n	%
(I) Infection		
Lung	47	46.08
Unspecified site	27	26.47
Others	11	10.78
Human Immunodeficiency Virus (HIV)-related	5	4.90
Urinary tract	4	3.92
Gastrointestinal	4	3.92
Central nervous system	4	3.92
Total	102	100
(II) Malignancy		
Gastrointestinal	12	25.00
Lung	9	18.75
Breast	6	12.50
Lymphoma and leukaemia	5	10.42
Upper aerodigestive tract	3	6.25
Others	7	14.58
Unknown	6	12.50
Total	48	100

Table V: Systemic therapy, severity of psoriasis and causes of mortality

Systemic therapy	Infection n (%)	Other causes of death n (%)	χ^2 statistic (df)	P value[a]
Yes	29 (37.2)	49 (62.8)	0.546	0.460
No	71 (32.6)	147 (67.4)	(1)	
Systemic therapy	**Malignancy n (%)**	**Other causes of death n (%)**	**χ^2 statistic (df)**	**P value[a]**
Yes	12 (15.4)	66 (84.6)	0.003	0.958
No	33(15.1)	185 (84.9)	(1)	
Systemic therapy	**Cardiovascular disease n (%)**	**Other causes of death n (%)**	**χ^2 statistic (df)**	**P value[a]**
Yes	23 (29.5)	55 (70.5)	1.012	0.314
No	78 (35.8)	140 (64.2)	(1)	
Severity	**Cardiovascular disease n (%)**	**Other causes of death n (%)**	**χ^2 statistic (df)**	**P value[a]**
Yes	24 (30.0)	56 (70.0)	1.686	0.194
No	62 (38.5)	99(61.5)	(1)	

*Result was based on available information
[a]Chi-squared test

Hypertension, diabetes mellitus, dyslipidaemia, ischaemic heart disease and cerebrovascular disease were risk factors that were significantly associated with overall mortality among psoriasis patients (p<0.001) (Table I). Four factors emerged as predictive factors of higher mortality in adult patients with psoriasis, namely age >40 years (age 41-60 years old Odds Ratio (OR) 2.70, 95% Confidence Interval (95%CI) 1.75, 4.18; age >60 years OR 7.46, 95%CI 4.62, 12.02), male gender (OR 1.72, 95%CI 1.33, 2.22), severe psoriasis with body surface area (BSA) >10% (OR 1.52, 95%CI 1.19, 1.96) and presence of at least one cardiovascular co-morbidity (OR 1.67, 95% CI 1.30, 2.14) (Table II). Age of onset of psoriasis (whether 40 years old and below or more than 40 years old) had a weak association with mortality (OR 1.32, 95%CI 1.00, 1.75, p=0.049) while there was no significant association between systemic treatment and mortality.

Out of 419 deaths, 301 cases (71.8%) had reported causes of death (Table III) in which the most common cause of death was infection (n=102, 33.9%), followed by cardiovascular causes (n=101, 33.6%) and malignancy (n=48, 15.9%). For the remaining 118 cases (28.2%), the medical causes of death could not be determined as the death certification had been done by police who had listed 'death due to natural causes'. The types of infections and malignancies among the patients who died are listed in Table IV. For lung infections, out of 47 patients, 43 had pneumonia (91.5% of lung infections) while four patients (8.5%) had tuberculosis. Four patients with central nervous system infections, of which three (75.0%) had meningitis or meningoencephalitis while one (25.0%) had a cerebellar abscess.

Further analysis showed there were no significant associations between systemic therapy and mortalities due to infections, malignancies or cardiovascular disease while there was no significant association between severity and cardiovascular causes of mortality (Table V).

DISCUSSION

This paper presents mortality data obtained from a national registry of psoriasis patients in Malaysia and examines the various factors involved. According to the data from the Ministry of Health Malaysia, the leading cause of death in the Ministry of Health hospitals in 2012 were diseases of the circulatory system (24.69%), certain infectious and parasitic diseases (17.17%) and neoplasms (11.64%).[7] The frequency of deaths caused by infections, cardiovascular disease and neoplasms among psoriasis patients were higher than the statistics among the general population in Malaysia.

In a study by Wakkee *et al.*, patients with psoriasis had a significantly higher risk of infections requiring hospitalization, principally affecting the respiratory system, abdomen and skin although interestingly, systemic treatment for psoriasis was not found to be a significant contributory factor in this study.

Comorbidities such as diabetes mellitus, obesity (part of metabolic syndrome),[8,9] depression[10] and cerebrovascular disease;[11] lifestyle factors, and the systemic low-grade inflammation associated with psoriasis render patients more vulnerable to infections.[12] Although epidermal host defences in psoriatic skin are improved, this may not translate into a reduced rate of serious infections even for the skin.[12] On the other hand, the pathogenesis of psoriasis has been postulated to have links with focal infections.[13] Older age is also linked with decline in immune function and increased risk of mortality based on our findings.[14]

The increased risk of cardiovascular mortality after adjusting for risk factors,[3-6] is noted particularly in severe psoriasis and in younger patients.[15-17] The association between psoriasis and cardiovascular disease may be attributed to a combination of non-modifiable, modifiable and novel risk factors like elevated C-reactive protein (CRP) or hyperhomocysteinaemia.[18-22] The psoriatic march concept states that systemic inflammation in psoriasis leads to insulin resistance and endothelial dysfunction.[23]

Methotrexate and tumour necrosis factor inhibitors reduce the risk of cardiovascular-related morbidity and mortality. Conversely, cylosporine A increases the frequency of cardiovascular risk factors while methotrexate, cyclosporine A and acitretin have been linked with insulin resistance. Despite prior evidence, our data showed that the use of systemic treatment had neither a significant association with mortality in general nor causes such as infections, malignancies and cardiovascular disease. Thus, mortality was unlikely to be due to the adverse effects of therapy.

A meta-analysis by Pouplard *et al.* showed an increased risk of certain malignancies among psoriasis patients, namely respiratory tract cancers, upper aerodigestive tract cancers, urinary tract cancers, liver cancer, pancreatic cancer, non-Hodgkin lymphoma, squamous cell carcinoma, basal cell carcinoma and breast cancer.[24] A link between alcohol and smoking with the development of malignancies has been postulated. The use of treatment modalities such as phototherapy (PUVA), cyclosporine A and methotrexate may play a role in the development of non-melanoma skin cancers, particularly squamous cell carcinoma.[24]

Increased severity of psoriasis as defined by body surface area of >10% was associated with higher risk of mortality although not cardiovascular disease in particular. However, Armstrong *et al.* found that patients with severe psoriasis were at higher risk of cardiovascular mortality in addition to the increased risks of myocardial infarction and stroke.[25] Ideally, assessment of severity could utilise the Psoriasis Area and Severity Index (PASI) or the Physician Global Assessment (PGA) scores but these data were not available from our registry. Another limitation is that some of the death certifications were done by police, where the cause of death was stated as natural causes and the actual causes could not be determined in 28.2% of cases. Due to the retrospective nature of the study, the presence of lifestyle factors such as smoking or drinking and psychological comorbidities could not be determined. There was also possible selection bias as patients notified to the registry were mainly those attending Dermatology clinics who were more likely to have severe disease. Missing data was also present. More population-based studies with control groups may be needed to further assess the causes of mortality among psoriasis patients in the general Malaysian population.

Management of psoriasis patients should aim at controlling inflammation, approaching the patient holistically and monitoring comorbidities. Dermatologists can play a role as the 'gatekeeper' and refer to the relevant specialties such as cardiologists, rheumatologists or oncologists to manage the various comorbidities. Moreover, screening and prevention of cardiovascular risk factors and diseases plus joint deformities should be part of our approach to management. There is a potential role for the use of cardiovascular biomarkers for psoriasis patients beyond the research setting. As diabetes mellitus may also lead to immunosuppression, glycaemic control is an important issue to address.

CONCLUSION

Predictive factors of higher mortality among adult psoriasis patients include older age, male gender, severe disease with BSA>10%, and the presence of cardiovascular co-morbidities. Although cardiovascular diseases are well-known to cause significant morbidity and mortality among psoriasis patients, the role of infections and malignancy should not be overlooked. Control of comorbidities that may also increase the patients' risks of developing infections and tumours remain imperative in the approach towards the management of psoriasis. Adopting the 'treat to target' approach may also result in greater improvement in the severity of psoriasis, thus reducing risk of mortality.

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