

A Retrospective Cohort Study of Epidemiology and Clinical Outcome in Lichen Planus

Dear Editor,

Lichen planus (LP) is a chronic inflammatory, papulosquamous disease. A previous Singapore study reported that LP is more common in ethnic Indians.¹ Other studies have reported that LP may be associated with metabolic syndrome-related diseases, such as hyperlipidaemia^{2,3} and diabetes mellitus.^{4,5}

LP in Asians has not been well characterised, especially in Singapore which has a multiracial population. This retrospective cohort study aimed to assess the descriptive epidemiology of LP in Singapore, such as ethnicities, comorbidities, types of LP, and sites of involvement and its general outcome. This study also aimed to evaluate any associating factors with the disease outcome. This would be useful for the management of LP.

Materials and Methods

Study Population

All cases diagnosed as LP at a tertiary outpatient dermatology clinic between January 2004 and December 2010 were retrieved from electronic medical records (EMRs) using the International Classification of Diseases, 9th revision, (ICD-9) code 697.0. Cases were either diagnosed clinically only or based on both clinical and histological confirmation. Information such as demographic data of involvement, modes of treatment, comorbidities (diabetes mellitus, dyslipidaemia) were analysed as covariates and potential confounders. Diagnosis of diabetes mellitus and

dyslipidaemia were identified by either self-reported history or documented medications specific for each condition. The time interval from date of diagnosis to the date of first physician-reported clinical improvement during follow-up was noted for each patient to account for the varying follow-up duration. Patients were followed up every 2 to 4 months.

Statistical Analysis

Hazard ratio (HR), 95% HR confidence interval (CI), and *P* values were calculated to test the null hypotheses of the association between the various variables and clinical improvement during follow-up. A multivariate Cox proportional hazard regression with rate of improved outcome as the dependent variable was performed. The Statistical Package for Social Sciences (IBM SPSS Verson 22) was utilised to perform the analysis. A two-sided *P* value of <0.05 was considered statistically significant. The study was approved by our Institutional Review Board (IRB).

Results

Demographic Profile of Study Population

There were 814 patients diagnosed with LP between January 2004 and December 2010, with a mean age of 47.1 years and slight male predominance (52.9%). Indians were overrepresented (52.1%) in the study population, compared to Chinese (29.5%) and Malays (4.2%). Table 1 shows the ethnic composition of our study population and all new patients attending for skin diseases at the clinic.

Table 1. Demographics Characteristics of Our Study Population

Ethnic Group n (%)	Patients with Lichen Planus (n = 814)	New Patients Attending for Skin Diseases [†] (n = 385,492)	Singapore Population [‡] (n = 3,771,700)	<i>P</i> Value
Chinese	240 (29.5)	295,909 (76.8)	2,794,000 (74.1)	<0.001 [†] <0.001 [‡]
Malay	34 (4.2)	22,133 (5.7)	503,900 (13.4)	0.055 [†] <0.001 [‡]
Indian	424 (52.1)	33,008 (8.6)	348,100 (9.2)	<0.001 [†] <0.001 [‡]
Others*	114 (14.3)	34,441 (8.9)	125,800 (3.3)	<0.001 [†] <0.001 [‡]

*Refers to other minority ethnic groups.

[†]Dermatology clinic returns from 2004 to 2010.

[‡]According to the Singapore Population Census 2010.

Diagnosis and Clinical Features of Lichen Planus

LP was diagnosed by clinical features alone in 445 (54.7%) patients, and by both clinical as well as histological confirmation in 369 (45.3%) patients. LP involving only the skin affected 471 (65.9%) of the patients.

The most common morphologic variant was LP vulgaris (85.1%). The most common mode of treatment was topical steroids (82.2%), comprising 0.1% of betamethasone valerate cream/ointment or clobetasol cream/ointment for cutaneous LP and either triamcinolone oral paste or clobetasol ointment for oral LP. Table 2 shows the clinical features and treatment modalities.

Treatment Outcome

More than half of the patients (55%) demonstrated an improved outcome on follow-up. Table 3 shows the results of different variables and corresponding rates of improved outcome. The rate of improved outcome for the younger

(≤ 50 years old) population was 1.29 times that of the older (> 50 years old) population ($P = 0.007$; 95% CI, 1.07 to 1.56). Those with diabetes or hyperlipidaemia had a lower rate of improved outcome compared to those with no comorbidities (HR = 0.562; $P < 0.001$). In contrast, the rates of improved outcome did not differ significantly between the different ethnic groups, sites of improvement and treatment options.

A multivariate analysis with a Cox regression model was performed to ascertain the effects of age, gender, ethnic groups, types of LP, presence of diabetes mellitus and/or hyperlipidaemia, and treatment options on the rate of improved outcome. The Cox regression model was statistically significant ($\chi^2 (8) = 25.4$, $P = 0.001$). The presence of diabetes mellitus and/or hyperlipidaemia was associated with a lower rate of improved outcome compared to those without diabetes mellitus and hyperlipidaemia (HR = 0.603; 95% CI, 0.443 to 0.820; $P < 0.001$). Multivariate analysis did not reveal any statistically significant relationship between age groups, ethnic groups, types of LP (cutaneous LP vs oral LP), treatment options and the rate of an improved outcome.

Table 2. Clinical Features of LP

Characteristics	Patients with LP n (%)
Sites of involvement	714
Skin only	471 (65.9)
Skin and nails	17 (2.4)
Skin and oral mucous membrane	63 (8.8)
Oral mucous membrane	134 (18.8)
Genital mucous membrane	29 (4.1)
Types of LP	415
LP vulgaris	353 (85.1)
LP hypertrophic	17 (4.1)
LP atrophic	5 (1.2)
LP planopilaris	18 (4.4)
LP pigmentosus	12 (2.9)
Annular LP	1 (0.2)
Linear LP	5 (1.2)
LP pemphigoides	2 (0.5)
Bullous LP	1 (0.2)
Actinic LP	1 (0.2)
Treatment options*	
Topical steroids	669 (82.2)
Systemic steroids	118 (14.6)
Intralesional steroids	27 (3.3)
Topical calcineurin inhibitors	75 (9.3)
Systemic retinoids	6 (0.7)
Phototherapy	21 (2.6)

LP: Lichen planus

*Patients were allowed to have more than 1 response.

Discussion

In our study, more than half (52.2%) of the study population were ethnic Indians. There was an overrepresentation of Indians, considering the ethnic distribution of all new clinic attendees in the same time frame and that of the Singapore population in 2010. Based on the 2010 Singapore population census⁶ (Table 1), Indians made up only 9.2% of the Singapore population. This result was comparable to a local study in 1988, in which Indians consisted of 69% of the study population.¹ To date, there is no genetic, developmental, or environmental explanation that explicates Indians' predisposition to LP.

Atefi et al⁴ found that the duration of LP in patients with diabetes mellitus was significantly longer than those without such condition. Other studies^{2,3} have reported that hyperlipidaemia was associated with an increased prevalence of LP, in addition to affecting its clinical outcome.

In our study, we observed that diabetes mellitus and/or hyperlipidaemia were associated with a significantly lower rate of improved outcome. It has been postulated that the inflammatory nature of the metabolic syndrome conditions have a role in the pathogenesis of LP, a Th1 dominant disease similar to psoriasis.³ The pathologic glucose levels in diabetes mellitus not only inhibits the proliferation of keratinocytes and fibroblasts, but also causes apoptosis of endothelial cells and decreases vasodilation by blocking nitric oxide synthesis.⁷ Moreover, advanced glycation end products activates NF- κ B signalling pathway, resulting in the release of proinflammatory cytokines and increased

Table 3. Univariate and Multivariate Analysis of Variables and Rate of Improved Outcome

Variables	HR	95% CI	P Value	Adjusted HR	95% CI	P Value
Age						
≤50 years	1.29	(1.07, 1.56)	0.007	0.894	(0.724, 1.10)	0.295
>50 years	1.00					
Gender						
Male	1.21	(1.01, 1.46)	0.045	1.23	(1.01, 1.49)	0.430
Female	1.00					
Race						
Chinese	1.00		0.335	1.00		0.565
Malay	1.26	(0.776, 2.04)	0.353	1.08	(0.643, 1.81)	
Indian	0.988	(0.802, 1.22)	0.906	0.926	(0.732, 1.17)	
Others	1.26	(0.918, 1.73)	0.152	1.14	(0.818, 1.60)	
Comorbidities						
Diabetes and/or hyperlipidaemia	0.562	(0.423, 0.746)	<0.001	0.603	(0.443, 0.820)	0.001
No comorbidities	1.00					
Sites of involvement						
Mucosal surface involved	0.966	(0.797, 1.17)	0.725	0.932	(0.756, 1.15)	0.513
Mucosal surface not involved	1.00					
Treatment						
Systemic treatment	0.889	(0.692, 1.14)	0.889	0.861	(0.668, 1.11)	0.245
Topical treatments	1.00					

CI: Confidence interval; HR: Hazard ratio

intracellular oxidative stress.⁸ This increased oxidative stress may play a role in delaying clinical improvement in LP patients with concurrent metabolic-related syndromes such as hyperlipidaemia and diabetes mellitus.^{9,10}

Strengths and Limitations

This was a large study with more than 800 cases of mucocutaneous LP. The multiethnic study population meant that an analysis of the disease could be carried out on diverse ethnic groups. The main limitation of this study was its retrospective nature. In addition, clinical improvement was mainly a physician-reported outcome and it was not standardised with a scoring system in terms of area of involvement, severity, or a patient-reported quality of life index. The time to first clinical improvement of the patient was noted and analysed in the study to account for the varying follow-up duration. However, we could not eliminate bias from interval censoring and this study lacked data regarding frequency of relapse. Information on the severity of diabetes mellitus, hyperlipidaemia and presence of other metabolic syndrome parameters, such as hypertension and increased waist circumference, were not available in our records. Prospective cohort studies should be conducted to assess the relationships between metabolic syndrome and the clinical course of LP.

Conclusion

LP affects a disproportionate number of Indians in Singapore. Patients with concomitant diabetes mellitus and/or hyperlipidaemia experienced a lower rate of improved outcome. Age groups, ethnic groups, sites of involvement and treatment options did not significantly affect the rate of improved outcome.

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