



Assessing Effect of Infection in Each Season of the Year on Recurrence of Psoriasis: Using the Time-Dependent Coefficient Rates Model for Recurrent Event Data

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Psoriasis can be provoked or exacerbated by a variety of different environmental factors, particularly infections. This disease may occur frequently for a person. Therefore, it's placed in recurrent event category. Unfortunately, few studies have determined which factors are independently associated with psoriasis. We attempted to provide an estimate of the risk for psoriasis associated with a recent infectious disease in different seasons of year and to explore other potential risk factors. The current study was conducted at the Department of Dermatology, Imam Khomeini Hospital, Tehran University of Medical Sciences, between March 2006 and April 2014. A total of 160 patients with confirmed diagnosis of psoriasis were included in the analysis. The original outcomes of the study were recurrent event times. Time dependent rate model was applied to assess the estimate of the effect of infection in different seasons association with psoriasis recurrence and also investigate other affective factors. Up to 6 recurrences were observed during the study time, but only 10% of the patients experienced more than 3 recurrences. The results showed positive correlation between the impact of infection in cold weather and recurrence of psoriasis ($P < 0.001$). The risk increased with the reported history of any infectious disease. According to the results of model fitting, the impact of infection on recurrence of psoriasis was significantly different in different seasons, so that patients who had infections faced with a higher recurrence risk during the winter ($P < 0.01$). The patients with types of infections were more likely to experience psoriasis recurrence especially in the winter. Therefore it can be concluded that changes of season of year

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infections even streptococcal infection in cool weather may provide the progression of the psoriasis and the hazard of its recurrence.

Keywords: psoriasis, recurrent event, infection, time-dependent coefficient rates model

INTRODUCTION

Psoriasis is a common chronic inflammatory and hyperproliferative skin disease. It affects approximately 2% of the world's population with equal distribution among sexes(1). The etiology of psoriasis appears to be multifactorial, but evidence suggests T-lymphocyte-based immunopathogenesis (2,3). The disease does not threaten patient's life typically, but sometimes due to joint involvement cause inability. According to the current concept, psoriasis is a complex genetic disorder caused by the interplay of many different genes(4). Some candidate genes like p53 are suspected of being involved in the pathogenesis of the disease (5). Age of onset is often second to fourth decade and in people who have a family history, the disease in younger age begins. Unfortunately, accurate statistics on the prevalence of psoriasis is not available in Iran. Although a genetic basis exists, environmental triggers exacerbate symptoms. Various lifestyle factors (e.g. smoking, alcohol use, obesity and emotional stress) have been associated with its morbidity (3, 6-8). In the case of psoriasis, recent pharyngeal infection has been implicated (9). Chinese authors verified that patients of acute psoriasis have a high incidence of *Streptococcus hemolyticus* in their throats and raised titers of antistreptococcal M6 protein in their sera (10). Outbreaks in different parts of the world are recorded between one to three percent and according to the population of Iran country, there are between 1 to 3 million people with psoriasis approximately (11). In addition, the risk for an aggravation or an abrupt recurrence of this autoimmune disease is very high. In spite of the high incidence and recurrence rate of psoriasis in Iran, the etiological studies in this field are very sparse. In survival analysis nature of some events is such a manner which may occur several times to an individual or experimental unit. Such events are called recurrent events. Time-dependent coefficient rates model is a statistical analysis method that would be appropriate in situations where the effect of an exposure or covariates changes over time in recurrent event data settings. The aim of this study is to identify factors associated with recurrence of psoriasis and evaluate the effect of infection in different seasons of the year by using time-varying coefficients rates model.

METHODS

This research was conducted as a longitudinal study at dermatology department of Imam Khomeini Hospital of Tehran from March 2006 and April 2014, Iran. Only patients who had relapses leading to hospitalization and were regularly referred to the hospital were included. After a preliminary assessment, a total of 160 patients were identified. Interviews were performed by using a structured questionnaire. The data were collected on sex, place of residence, marital status, level of education, infection, personal and family history, occupation, smoking habits, stress and their current status information asked with a phone call to the patient or their family and other demographic characteristics including age at diagnosis, hypertension and clinicopathological characteristics measured at a pathobiology laboratory on each visit such as HDL, LDL and triglycerides were obtained from the hospital records. The current study was approved by the Ethical Committee of the Medical Science Faculty of Tarbiat Modares University.

In the current study the time-dependent coefficients rate model was applied to estimate infection effect on psoriasis relapse in different seasons of year:

$$d\mu_i(t) = \exp\{\beta^T Z_i(t) + \theta(t) W_i(t)\} d\mu_0(t)$$

In which $d\mu_0(t)$ is base rate function and $Z(t)$ is a vector of covariates that it is assumed that their effect on the response remains constant all along study. $W(t)$ is a variable that expected its effect on the response is different at different points in time. $\theta(t)$ are time-dependent coefficients related to $W(t)$ that is estimated by the third degree of B-spline functions.

$$\hat{\theta}(t) = \hat{\gamma}_0 + \sum_{k=1}^{m+3} \hat{\gamma}_k \tilde{B}_k(t)$$

In this regard, \tilde{B} are B-spline basis functions and m is the number of internal nodes. AIC criterion was used to determine the number of nodes. Therefore, first by using different nodes ($m=1,2,\dots,6$), different models were fitted and AIC index was calculated for each of them. Then number of nodes corresponding to the model with the lowest value of AIC was chosen. To test the difference in effect of infection on the psoriasis recurrence in different seasons of year Wald statistic was used:

$$Q_W = (\hat{\gamma}^*)' (Cov(\hat{\gamma}^*))^{-1} \hat{\gamma}^*$$

in which $\gamma^* = (\gamma_1, \dots, \gamma_{m+3})'$, if the variable effect of interest $W(t)$ be constant over time, then Q_W statistic will have a chi-square distribution with $m+3$ degrees of freedom. We used `bs` and `coxph` functions in R software version 3.3 to analysis data.

RESULTS

A total of 160 patients who had been diagnosed with psoriasis were studied. The mean \pm SD age at diagnosis in year was 43.4 ± 17.29 . The demographical characteristics of the patients are presented in Table 1. The number of recurrences of the diseases is shown by plot in Figures 2. The estimated results using the time-dependent coefficients rates model are presented in Table 1. Based on the obtained result, there was no significant relationship at 5% level between the factors gender, different phenotype of psoriasis, age, hypertension, eating habits, year of study entry and hazards of recurrence leading to hospitalization ($p > 0.05$). The risk of recurrence of psoriasis was also increased in subjects who reported a history of a recent infectious episode. Psoriasis also increases chances of increasing blood levels of cholesterol, LDL, and triglycerides. Table 2,3 shows the results of the time-dependent coefficients rate model.

Table 1. The demographical characteristics of the patients

Variable	Patients, (n = 160)	
	Mean ± SD	No. (%)
Gender		
Male	47± 17.22	89 (55.6%)
Female	40.87±16.92	71 (44.4%)
Marriage		
Married		113 (62/70%)
Single		47 (37/29%)

Table 2. Results of the fitting time-dependent coefficients rates model for recurrence rate in patients with psoriasis

Risk factors	Relative rate	95% confidence interval	P-value
history of	1.07	(1.04,3.78)	0.043
Marital status	0.62	(0.43,1.66)	0.022
Smoking**	2.01	(1.54,2.46)	0.044
stressful life events	1.82	(0.79,2.27)	0.04
Season of relapse	2.95	(2.34,8.45)	0.001
family history of	1.47	(0.99,2.28)	0.03
HDL	0.34	(0.19,2.11)	0.2
LDL	1.14	(1.0,1.23)	0.03
Triglycerides	1.45	(0.87,2.32)	<0.001

** : Patients who smoke than those who do not smoke

* : Single patients than married patients

In order to evaluate the effect of infection in different seasons of year, the time-dependent coefficients rates model was used and the results are given in table 3. According to the result obtained, the effect of this factor isn't significant in summer. With being cold weather, infection effect in recurrence rate about 6 times increase in autumn and it increase up to 7.5 times in winter, which means that the disease is more likely to recur in patients with higher infection in winter. In addition, Wald test results showed that the effect of infection on recurrence of psoriasis vary significantly in different seasons ($p < 0.01$).

Table 3. The demographical characteristics of the patients

Seasons of year	Relative Rate of Recurrence	95% confidence interval	P-value
Spring	2.79	(0.85,5.87)	0.03
Summer	1.66	(0.17 ,6.69)	0.16
Autumn	6.45	(3.67 ,11.11)	<0.001
Winter	7.11	(5.40 ,11.60)	<0.001

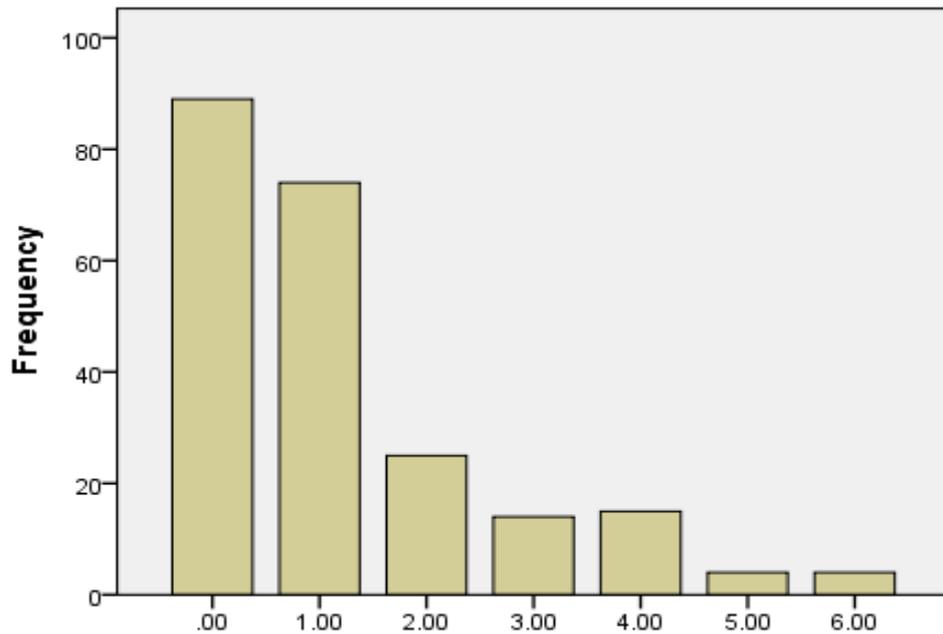


Figure 3. Number of recurrent psoriasis

DISCUSSION

Recent reports revealed a high rate of psoriasis incidence in Iran. In addition, high recurrence rate of psoriasis makes it one of the important concerns of dermatology (12). Therefore the current study was conducted to evaluate the prognostic factors of psoriasis recurrence and its association with infection. The present study utilized a new statistical methodology, the time-dependent coefficients rates model to examine whether changes in seasons over time was associated with effect of infection on recurrence in psoriasis patients. The study showed no significant prognostic factor related to hazard of psoriasis recurrence. However single patients had a 62% more rate of recurrence than the married ones (RR=0.62, P =0.02). This study provides evidence that hazard of psoriasis recurrence is strongly associated with a family history of psoriasis, indexes of psychological stress and recent pharyngitis. Medical histories were collected in a standardized way and only infectious episodes diagnosed by a specialist were taken into account. The life stressful events examined (e.g. death of a close family member). A long-held belief supported by fairly convincing clinical

and immunologic evidence associates psoriasis with infection (13). Our study suggests that recent pharyngeal infection is associated with a 7-fold increase in the risk for a first episode of psoriasis compared with subjects not reporting such a history. The study does not provide any information on the infectious agents responsible. There is evidence that an immunologic mechanism is involved in the triggering of recurrence of psoriasis by streptococcal infection. It is likely that genetic factors are also involved. Familial cases of psoriasis have been described (14). Clinical studies suggest that psoriasis is made worse by stress in approximately 30% to 40% of cases (6, 15). There is some evidence that in humans and experimental animals stress may suppress or enhance immune functions, depending on the immune variables under consideration and the temper of the stressor. In conclusion, we have documented a strong association between relapse of psoriasis, family history of psoriasis, index of stress, and recent acute pharyngitis. Trigger and perpetuating factors in psoriasis should be further explored in epidemiologic studies. Cause of psoriasis relapse is complicated and physicians don't know a lot about why things like stress and upper respiratory infections make psoriasis worse in some patients, however, that psoriasis is related to your immune system. Although psoriasis triggers can vary from patient to patient, finding out what reasons your skin to flare up is one of the best methods to try to control the condition. In cold weather, taking a trip to the hot and dry areas might be a good idea during the winter months, as because the sun's ultraviolet light turns off the skin's immune system, which is overactive in people with psoriasis. Cold winter weather makes psoriasis worse, rather because sunlight makes it better. Along with the cold temperatures, the drier air and also shorter days can flare relapse of psoriasis and about respiratory infections, colds and other infections, specially strep throat, activate the immune system and can stimulus psoriasis to flare. About diet, studies haven't shown any beneficial effects of taking nutritional supplements for psoriasis, but avoiding specified foods may decrease inflammation of psoriasis, because people with psoriasis have an increased risk for cardiovascular disease. While the link between psoriasis and heart disease is not yet obvious, psoriasis patients are more probable to have risk factors like hypertension and high cholesterol. All available methods in the literature were defined for univariate time-to-event settings. The proposed approach is useful in estimating time-varying coefficients in the recurrent time-to-event data. If the purpose of the study is to estimate the overall effect of infection on recurrence of psoriasis, proportional rate model provides a reasonable estimate but if the goal is an accurate estimate of the effect of infection on recurrence of psoriasis for different seasons. Using this model and consequently assuming fixed effect is not correct. Amorim and colleagues used rate model with time-dependent coefficients for the first time and could show the effect of vitamin A on reducing diarrhea has been dropping over time (16). Whereas other studies did not find significant reductions in either the incidence or the mean daily prevalence of diarrhea, so using the proportional rate model in conditions that when effect of the interest variable under study on the occurrence of events vary at different time points can lead to be ignored or reduce visibility of variable's effect. This methodology may be potentially useful for describing the behavior of many other exposures or covariates associated with research questions in epidemiology and public health. Therefore, as part of beneficial medical care, psoriasis patients should be encouraged to identify and manage their modifiable

cardiovascular risk factors. In the present study an increase in blood levels, triglyceride increases recurrence rate up to 14%, that this finding is consistent with the results of a study gained in Japan by Seshima in 1995 (17). In a study by Azizzadeh in 2000 (18) was reported significant difference that coordinate with the results of our study. It seems that these differences are due to biological and climatic conditions as well as conditions different nutritional. Therefore, we recommend checking all patients with psoriasis, regardless of their disease severity. In addition, we strongly recommend in psoriasis patients with developing a sore throat, get it treated. Long-term antibiotics may be a choice for someone who has psoriasis and repeated sore throats.

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REFERENCES

1. Raychaudhuri SP, Farber EM. The prevalence of psoriasis in the world. *Journal of the European Academy of Dermatology and Venereology* : JEADV. 2001 Jan;15(1):16-7. PubMed PMID: 11451313.
2. Giardina E SC, Novelli G. The psoriasis genetics as a model of complex disease. *Curr Drug Targets Inflamm Allergy*. 2004;3:129-36.
3. Kormeili T, Lowe NJ, Yamauchi PS. Psoriasis: immunopathogenesis and evolving immunomodulators and systemic therapies; U.S. experiences. *The British journal of dermatology*. 2004 Jul;151(1):3-15. PubMed PMID: 15270867.
4. Guilhou JJ MJ. New hypotheses in the genetics of psoriasis and other "complex" diseases. *Dermatology*. 2008 (216):87-92.
5. Yazici AC KA, Ozen O, EkSio2lu M, Ustün H. Expression of p53 in lesions and unaffected skin of patients with plaque-type and guttate psoriasis quantitative comparative study. *J Dermatol*. 2007 (34):367-74.
6. Higgins EM PT, du Vivier AW. Smoking, drinking and psoriasis. *The British journal of dermatology*. 1993 (28):730-2.
7. Naldi L CL, Linder D et al. Cigarette smoking, body mass index, and stressful life events as risk factors for psoriasis: result from an Italian case-control study. *J Invest Dermatol*. 2005 (127):61-7.
8. Naldi L PF, Brevi A et al. Family history, smoking habits, alcohol consumption and risk of psoriasis. *Br J Dermatology*. 1992 (127):212-7.
9. Naldi L PL, Parazzini F, Carrel CF. Psoriasis Study Group of the Italian group for Epidemiological Research in Dermatology. Family history of psoriasis, stressful life events and recent infectious disease are risk factors for a first episode of acute guttate psoriasis: result of a case-control study. *J Am Acad Dermatol*. 2001 (44):433-8.
10. Zhao G FX, Na A et al. Acute guttate psoriasis patients have positive streptococcus hemolyticus throat cultures and elevated antistreptococcal M6 protein titers. *J Dermatol*. 2005 (32):91-6.
11. Liu Y KJ, Bowcock AM. Psoriasis: genetic associations and immune system changes. *Genes and immunity*. PubMed PMID: 17093502. 2007;8(1):1-12.
12. Esmaily N EA, Noormohammadpour P, Baiagouy I, Sayanjali, S. Psoriasis Recurrence Rate and its Relationship with Initial Corticosteroid Dose. *Iran J Dermatol*. 2010;13(4):118-21.
13. Lewis HM BB, Bokth S, Powles AV, Garioch JJ, Valdimarsson H ea. Restricted T-cell receptor V-beta gene usage in the skin of patients with guttate and chronic plaque psoriasis. *The British journal of dermatology*. 1993 (129):514-20.

14. Bolton GG DC. A family outbreak of acute guttate psoriasis. *Arch Dermatol.* 1990 (126):1523-4.
15. Gupta MA GA, Kirkby S, Schork NJ, Gorr SK, Ellis CN, et al. A psychocutaneous profile of psoriasis patients who are stress reactors: a study of 127 patients. *Gen Hosp Psychiatry.* 1989 (11):166-73.
16. Amorim LD CJ, Zeng D, Barreto ML. Regression splines in the time-dependent coefficient rates model for recurrent event data. *Stat Med.* 2008 (7):5890-906.
17. Seishima M SM, Mori S, Noma A. Serum lipid and apolipoprotein levels in patients with psoriasis. *The British journal of dermatology.* 1994 (130):738-7.
18. Azizzadeh M GR, Sharafi M. Serum lipids profiles in psoriatic patients. *Koomesh.* 2010 (12):307-12.