Evaluation of Atopic Dermatitis and Infectious Disorders Using Sequential Pattern Mining

Ju Hee Han  
Department of Dermatology, Seoul St. Mary’s Hospital, College of Medicine, The Catholic University of Korea

Jae Woong Yoon  
Department of Business Management, Kwangwoon University

Chul Hwan Bang  
Department of Dermatology, Seoul St. Mary’s Hospital, College of Medicine, The Catholic University of Korea

Jae Hun Chun  
Department of Business Management, Kwangwoon University

Jun Young Lee  
Department of Dermatology, Seoul St. Mary’s Hospital, College of Medicine, The Catholic University of Korea

Young Min Park  
Department of Dermatology, Seoul St. Mary’s Hospital, College of Medicine, The Catholic University of Korea

Suk Jun Lee  
Department of Business Management, Kwangwoon University

Ji Hyun Lee (✉ ejee@catholic.ac.kr)  
Department of Dermatology, Seoul St. Mary’s Hospital, College of Medicine, The Catholic University of Korea

Research Article

Keywords: atopic dermatitis, barrier, dermatology, epidemiology, infections

DOI: https://doi.org/10.21203/rs.3.rs-129587/v1

License: ☑️ This work is licensed under a Creative Commons Attribution 4.0 International License. Read Full License
Abstract

Atopic dermatitis (AD) is a chronic inflammatory skin disease related with abnormal immune response and epidermal barrier function impairment. The aim of our study was to estimate the association between AD and infectious disorders in real world. We analyzed population-based data from 2010 to 2013 using National Health Insurance Service. Sequential pattern mining (SPM) was used to identify comorbid infectious diseases and onset duration of the comorbidities. Patients with AD were at higher risk for molluscum contagiosum (adjusted odd ratio (aOR) 5.273), impetigo (aOR 2.852), chicken pox (aOR 2.251) and otitis media (aOR 1.748), eczema herpeticum (aOR 1.292), viral wart (aOR 1.105). Our study suggests that AD is associated with increased risk of infectious disorders. In particular, care should be taken for early diagnosis of comorbidity and appropriate management.

Introduction

Atopic dermatitis (AD) is a relatively common, relapsing, chronic inflammatory skin disorder, and the prevalence of AD in children worldwide ranges from 15–30% and in adults worldwide ranges from 2–10%.(1–3) AD is known to be related to impaired function of the epidermal barrier and abnormality of the skin innate immune response.(4, 5) Clinically, AD is related to a chronic itching sensation, sleep disturbance and impaired daily, school and work life, and patients with AD are also susceptible to cutaneous and noncutaneous infections. According to previous studies, the increased risk of cutaneous and noncutaneous infections in AD is related to impaired epidermal function, abnormal systemic immune function, decreased antimicrobial peptides and immunosuppressive agent use for AD management.(6)

Compared to other association rule mining methods, sequential pattern mining (SPM) is a well-designed method for analyzing multiple sequential data sets with frequent association rules.(7, 8) SPM is based on and used in the retail industry to analyze transaction history at the point of sale. However, in the medical field, SPM could be applied to identify frequent patterns or behaviors that appear in a dataset, and it is also useful for identifying signs of concomitant diseases when there are multiple diseases in a patient’s medical record.

Many reports have demonstrated that AD patients are more susceptible to infectious disorders than healthy controls. However, there have been few studies regarding the time to the onset of these cutaneous and extracutaneous infectious disorders after the diagnosis of AD. The aim of our study was to investigate the association between AD and infectious diseases in the real medical environment through a population-based study using SPM.

Results

Baseline characteristics of the study population
A total of 70,205 AD patients were included from HIRA database. Table I shows the number, age and sex of patients with AD. The total number of male patients was 32,443, and the total number of female patients was 37,762. The number of patients aged 0 to 4 was 18,465, which showed the highest frequency, followed by patients aged 5 to 9, who numbered 9,814.

**Risk of infectious disorders in AD patients**

Table II shows the frequencies of impetigo, EH, chicken pox, herpes zoster, viral wart, molluscum contagiosum, viral conjunctivitis, and otitis media among individuals with AD. In addition, Table II shows the results of univariate and multivariate logistic regression analyses of the association between AD and infectious disorders. Based on the results for each code, patients with AD were at the highest risk for molluscum contagiosum (odds ratio [OR] 7.118, 95% confidence interval [CI] 6.932–7.310). Furthermore, the risks of impetigo (OR 3.352, 95% CI 3.252–3.455), chicken pox (OR 3.212, 95% CI 3.044–3.389), otitis media (OR 2.546, 95% CI 2.492–2.602), EH (OR 1.372, 95% CI 1.229–1.531), and viral wart (OR 1.077, 95% CI 1.022–1.135) were higher in AD patients than in controls. After age and sex adjustment, the risk remained higher in AD patients than in controls. Molluscum contagiosum showed a 5.273 times higher risk in AD patients than in controls, which also showed the highest risk after the adjustment.

The risk of herpes zoster decreased by 55.1% (95% CI 0.426–0.474) in patients with AD compared with that in the reference group individuals.

**Sequence patterns between AD and infectious disorders**

Figure 1 shows the sequence patterns between AD and infectious disorders and the disease duration extracted through SPM. The numbers in parentheses indicate the data for each disease.

The comorbidity association rule AD $\Rightarrow$ impetigo represents the percentage of patients with impetigo among patients with AD. The term duration points out the time (average number of days) it takes for a patient with AD to be diagnosed with impetigo.

The comorbidity of 1.06% for the association of AD $\Rightarrow$ molluscum contagiosum was the highest value among all the association rules, followed by values of 0.88%, 0.84%, 0.58%, 0.39%, 0.21%, 0.16% and 0.03% for the association rules of impetigo, otitis media, viral conjunctivitis, chicken pox, herpes zoster, viral wart, EH, and respectively. The duration of 77.42 days for the association rule of AD $\Rightarrow$ molluscum contagiosum was the shortest onset duration, followed by 85.59, 99.17, 118.85, 123.95, 146.22, 157.67, and 164.43 days for the association rules of impetigo, otitis media, chicken pox, viral conjunctivitis, EH, herpes zoster, and viral wart, respectively.

**Discussion**

This nationwide population-based cohort study evaluated the comorbidity between AD and infectious disorders using SPM. Our study also investigated the onset duration to infectious disorders from AD. According to our results, there was a significantly greater risk of infectious disorders in patients with AD
than in individuals without AD. Among the infectious disorders, molluscum contagiosum showed the highest increased risk in AD patients compared to that in controls. Furthermore, the time to first diagnosis duration of infectious disorders, especially molluscum contagiosum, was relatively shorter in patients with AD than in patients without AD, which was approximately 2 months after the diagnosis of AD.

In our study, the percentage of new-onset infectious disorders in patients with AD was defined as confidence. As the value of the parameter “confidence” is similar to comorbidity in epidemiology, we considered the value of confidence to serve as a value of comorbidity. In addition, the parameter “onset duration” is, in other words, the time to first diagnosis.

According to previous reports, AD predisposes patients to cutaneous and extracutaneous infectious disorders. Similar to those reports, our results suggest that AD increases the risk of infectious disorders, such as molluscum contagiosum, impetigo, viral wart, EH, viral conjunctivitis and otitis media. Previous studies suggest that bacterial infection is the most common infection and that Staphylococcus aureus is by far the most common bacterial infection in AD. The suggested mechanism for increased bacterial infection is barrier dysfunction, immune dysregulation, low antimicrobial peptides, increased bacterial colonization and the use of immunosuppressant medications for the management of AD.

According to our study, AD patients were at a 2.8-fold higher risk for impetigo than controls, which resembled the results of a previous cohort study. A previous cohort study from the USA that evaluated three million subjects under 18 years old showed that impetigo developed 55% more often in AD patients than in controls after adjusting for age and sex.

A previously reported study suggested that AD in children is related to recurrent ear infections as well as other bacterial disorders. A USA population-based study suggested that recurrent ear infection increased 1.33-fold in patients with AD. Our data show that the risk of otitis media was 1.75-fold higher in AD patients than in non-AD patients, which is consistent with prior data. According to our data, the comorbidity of otitis media was 0.84, and the onset duration was 99.17 days.

Similar to in other reports, skin viral infections, such as molluscum contagiosum, viral wart, herpes simplex infection, especially EH, chicken pox and viral conjunctivitis, increased in AD. The epidermal skin barrier defect, innate and adaptive immune dysfunction, decreased antimicrobial peptides, increased skin pH and Th2 cytokines are considered enhancing factors for increased risk of viral infection in AD patients.

In our results, the highest risk among viral infections in AD patients was that for molluscum contagiosum. In a case-control study with pediatric patients that analyzed the epidemiology and predisposing factors for molluscum contagiosum, patients with AD with local cellular immune dysregulation and an impaired skin barrier had a major incidence of molluscum contagiosum. In addition, other reports observed an increased prevalence of AD in children with molluscum contagiosum. Patients with AD are reported to not only have more molluscum contagiosum but also have more severe and widespread disease than individuals without AD. In accordance with prior studies, our
results showed a 5.2-fold increase in the risk of molluscum contagiosum in AD patients after adjusting for age and sex, which was the highest result in this study, and a comorbidity of 1.06%. The onset duration of molluscum contagiosum was 77.42 days, which was the earliest among the infectious disorders.

Our results showed that the risk of chicken pox was increased by 2.251-fold in patients with AD compared with that in patients without AD, and the confidence of chicken pox was 0.39%. Similar to our results, a previous study of childhood AD in the USA also reported risk of chicken pox that was 1.19 times higher in AD patients than in individuals without AD.(13) In addition, another study on adult AD in the USA showed a 1.31-fold increase in the risk of chicken pox in AD patients.(4) In the case of herpes zoster, our results indicate that AD patients have a 58% lower risk than normal controls, and the confidence was 0.213%. Few studies have confirmed a correlation between AD and herpes zoster. A previous population-based case-control study with children demonstrated that the risk of herpes zoster is increased in asthma patients, which is contrary to our data.(20)

According to our study, the risk of viral wart was 1.105 times higher in AD patients than in individuals without AD, and the confidence was 0.16%. The onset duration was approximately 5–6 months after the AD diagnosis. It is known that warts can spread more easily in the setting of AD.(21) In one study, warts and atopic dermatitis in children were accompanied by a higher number of infections and food allergies and a higher chance of hay fever and asthma than either condition alone.(13) According to this previous study, AD without other atopic diseases had slightly lower odds of warts (0.91 [95% CI, 0.90–0.92]) than controls, which was different from our study. However, AD with other atopic diseases showed an increased risk of warts (1.83 [95% CI, 1.82–1.84]).

The confidence of EH was 0.032%, which was slightly lower than that for other infectious disorders. However, the risk of EH was 1.292 times higher than that for controls. EH, which is caused by herpes simplex virus (HSV), is a potentially serious complication of AD that shows generalized vesicles with general symptoms, such as viremia, fever and lymphadenopathy. HSV exposure is common in the general population, which is present in approximately 60% of the adult population and 20% of children. However, according to other studies, only 3% of AD patients develop EH, and compared with AD patients without EH, patients with AD who have EH seem to have more severe AD, early onset of AD and increased accompanying atopic diseases.(6) Although the comorbidity of EH in AD patients is low, as the clinical manifestation of EH in AD patients tends to appear more widespread and severe, we should always keep in mind the seriousness and risk of EH in AD patients.

This study has some limitations. First, the data were collected from the NHIS claim database, and data such as smoking, physical activity, and family history were not available in our study. Second, there are some limitations in that our study was a retrospective cohort study. In addition, it is also possible to underestimate the diagnosis if the disease is mild and if the patient does not visit the medical center. Third, our study has limitations in that there is no information on each infectious species; however, one of the strengths of the study is that we analyzed all the bacterial, and viral infections.
The major strength of our study is that the data we used are maintained by the government or public agencies that provide national health information, and the data are thus standardized and stable. Additionally, we used a large sample size, the sample was representative of the entire country, and our study has the advantage of including all age groups, while most of the existing studies were conducted by surveys, interviews or with a small number of subjects. Finally, for the first time, the correlation between AD and infectious diseases was confirmed using SPM, and comorbidity, risk and onset duration were analyzed.

In conclusion, our study demonstrates that AD could increase the risk of infectious disorders, and these findings might be meaningful for early diagnosis and also for management. The early detection and treatment of infectious disorders in AD patients will prevent the aggravation of AD. In particular, care should be taken because of the high relevance of AD with impetigo, molluscum contagiosum and otitis media, and these results may help with prevention of worsening of disease and appropriate management in AD patients.

**Methods**

**Data source and study population**

We obtained population-based data from the National Health Insurance Service (NHIS) of Korea from January 1, 2010 to December 31, 2013. The entire Korean population is covered by the NHIS. In 2013, 97.2% (n = 49,989,620) of the population was covered by the NHIS database, and the remaining 2.8% (n = 1,458,871) were covered by the healthcare support system. NHIS claim data provides a relatively standardized, stratified one million-person sample (n = 1,062,018) from the NHIS database, which uses the International Classification of Disease, Tenth Revision, Clinical Modification (ICD-10-CM) codes. We extracted the study population from the NHIS claim database and anonymized all the data, which was provided to the researcher with the exception of the patient’s personal information. This study was approved by the Ethics Committee of Seoul St. Mary’s Hospital, the Catholic University of Korea (approval no. KC19ZESI0664).

**Identification of AD and infectious disorders**

Patients with AD and cutaneous and extracutaneous disorders were identified using ICD-10 (AD [L20], impetigo [L01], eczema herpeticum (EH) [B00.0], chicken pox [B01], herpes zoster [B02], viral wart [B07]), molluscum contagiosum [B08], viral conjunctivitis [B30] and otitis media [H65 + H66]) diagnostic codes. AD patients were defined as those who were diagnosed with ICD-10 code L20. Patients diagnosed with at least one infectious disorder in 2009 were excluded to evaluate the incidence of infectious diseases newly arising in AD.

**Statistical analysis**

We compared the occurrence of each infectious disorders in patients with AD and control group with logistic regression. Gender and age adjusted odds ratios (aORs) and 95% confidence intervals (CIs) were
obtained using multivariable logistic regression model. Data were analyzed using SAS Enterprise Miner version 13.2 (SAS Institute, Cary, NC, USA). A value of $P < 0.05$ was considered statistically significant.

**SPM**

We used SPM to evaluate the relationship between AD and infectious disorders by time differences, and the parameters for the SPM were based on the values of the confidence, which were defined as the probabilities of occurrence, and the duration values, which were defined as the average occurrence times. In this analysis, age, sex, ICD-10 codes, and date were used as variables, and we used SAS Enterprise Miner version 13.2 (SAS Institute) to identify the sequential pattern of the diseases.

**Abbreviations**

AD: Atopic dermatitis

SPM: Sequential pattern mining

HIRA: Health Insurance Research and Assessment Agency

NHIS: National Health Insurance Service

ICD: International Classification of Disease

EH: Eczema herpeticum

HSV: Herpes simplex virus

OR: Odds ratio

CI: Confidence interval

**Declarations**

**Acknowledgment**

This study was supported by Research Fund of Seoul St.Mary’s Hospital, The Catholic University of Korea. (ZC19RISI0004)

**Author contribution**

All authors of this article have directly participated in the planning, execution, or analysis of the study. All authors of this paper have read and approved the final version submitted.

**Role of the funding source**
Funding source(s) had no involvement in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the article for publication.

Informed consent
None

References

1. Silverberg JI. Public health burden and epidemiology of atopic dermatitis. *Dermatol Clin* 2017;35:283–289.
2. Garg N, Silverberg JI. Epidemiology of childhood atopic dermatitis. *Clin Dermatol* 2015;33:281–288.
3. Lee JH, Han KD, Kim KM, Park YG, Lee JY, Park YM. Prevalence of atopic dermatitis in Korean children based on data from the 2008–2011 Korean national health and nutrition examination survey. *Allergy Asthma Immunol Res* 2016;8:79–83.
4. Strom MA, Silverberg JI. Association between atopic dermatitis and extracutaneous infections in US adults. *Br J Dermatol* 2017;176:495–497.
5. Lee JH, Son SW, Cho SH. A comprehensive review of the treatment of atopic eczema. *Allergy Asthma Immunol Res* 2016;8:181–190.
6. Sun D, Ong PY. Infectious complications in atopic dermatitis. *Immunol Allergy Clin North Am* 2017;37:75–93.
7. Tai YM, Chiu HW. Comorbidity study of ADHD: applying association rule mining (ARM) to national health insurance database of Taiwan. *Int J Med Inform* 2009;78:e75-83.
8. Bang CH, Yoon JW, Lee HJ, Lee JY, Park YM, Lee SJ et al. Evaluation of relationships between onychomycosis and vascular diseases using sequential pattern mining. *Sci Rep* 2018;8:17840.
9. Leyden JJ, Marples RR, Kligman AM. Staphylococcus aureus in the lesions of atopic dermatitis. *Br J Dermatol* 1974;90:525–530.
10. Bath-Hextall FJ, Birnie AJ, Ravenscroft JC, Williams HC. Interventions to reduce *Staphylococcus aureus* in the management of atopic eczema: an updated cochrane review. *Br J Dermatol* 2010;163:12–26.
11. Fenner J, Silverberg NB. Skin diseases associated with atopic dermatitis. *Clin Dermatol* 2018;36:631–640.
12. Silverberg JI, Simpson EL. Association between severe eczema in children and multiple comorbid conditions and increased healthcare utilization. *Pediatr Allergy Immunol* 2013;24:476–486.
13. Silverberg JI, Silverberg NB. Childhood atopic dermatitis and warts are associated with increased risk of infection: a US population-based study. *J Allergy Clin Immunol* 2014;133:1041–1047.
14. Wollenberg A, Wetzel S, Burgdorf WH, Haas J. Viral infections in atopic dermatitis: pathogenic aspects and clinical management. *J Allergy Clin Immunol* 2003;112:667–674.
15. Ong PY, Leung DY. Bacterial and viral infections in atopic dermatitis: a comprehensive review. *Clin Rev Allergy Immunol* 2016;51:329–337.

16. Cai SC, Chen H, Koh WP, Common JE, van Bever HP, McLean WH et al. Filaggrin mutations are associated with recurrent skin infection in Singaporean Chinese patients with atopic dermatitis. *Br J Dermatol* 2012;166:200–203.

17. Kakourou T, Zachariades A, Anastasiou T, Architectonidou E, Georgala S, Theodoridou M. Molluscum contagiosum in Greek children: a case series. *Int J Dermatol* 2005;44:221–223.

18. Dohil MA, Lin P, Lee J, Lucky AW, Paller AS, Eichenfield LF. The epidemiology of molluscum contagiosum in children. *J Am Acad Dermatol* 2006;54:47–54.

19. Osio A, Deslandes E, Saada V, Morel P, Guibal F. Clinical characteristics of molluscum contagiosum in children in a private dermatology practice in the greater Paris area, France: a prospective study in 661 patients. *Dermatology* 2011;222:314–320.

20. Kim BS, Mehra S, Yawn B, Grose C, Tarrell R, Lahr B et al. Increased risk of herpes zoster in children with asthma: a population-based case-control study. *J Pediatr* 2013;163:816–821.

21. Silverberg NB. Pediatric warts: update on interventions. *Cutis* 2019;103:26;27;28;29;30;E22;E23;E24.

**Tables**

**Table I.** Demographics of the study population.
**Table II.** The 3-year risk, frequency and confidence of infectious disorders in atopic dermatitis patients.

| Age group | Total (n) |
|-----------|-----------|
| Total     | 70,205    |
| 0-4       | 18,465    |
| 5-9       | 9,814     |
| 10-14     | 6,786     |
| 15-19     | 4,852     |
| 20-29     | 3,564     |
| 30-39     | 2,703     |
| 40-44     | 3,176     |
| 45-49     | 2,779     |
| 50-54     | 2,935     |
| 55-59     | 2,586     |
| 60-64     | 2,819     |
| 65-69     | 2,556     |
| 70-74     | 1,837     |
| 75-79     | 1,549     |
| 80-84     | 1,559     |
| 85+       | 2,225     |

| Sex       | Total (n)   |
|-----------|-------------|
| Male      | 32,443 (46.21%) |
| Female    | 37,762 (53.79%) |
| Condition                          | Confidence (%) | Univariate OR (95% CI) | \( P \) value | Age-sex adjusted aOR (95% CI) | \( P \) value |
|-----------------------------------|----------------|-------------------------|--------------|------------------------------|--------------|
| Impetigo (L01)                    | 0.88           | 3.352 (3.252 – 3.455)   | <0.001       | 2.852 (2.766 – 2.942)        | <0.001       |
| Eczema herpeticum (B00.0)         | 0.032          | 1.372 (1.229 – 1.531)   | <0.001       | 1.292 (1.156 – 1.444)        | <0.001       |
| Chicken pox (B01)                 | 0.387          | 3.212 (3.044 – 3.389)   | <0.001       | 2.251 (2.131 – 2.377)        | <0.001       |
| Herpes zoster (B02)               | 0.213          | 0.449 (0.426 – 0.474)   | <0.001       | 0.422 (0.4 – 0.445)          | <0.001       |
| Viral wart (B07)                  | 0.159          | 1.077 (1.022 – 1.135)   | <0.001       | 1.105 (1.048 – 1.165)        | <0.001       |
| Molluscum contagiosum (B08)       | 1.057          | 7.118 (6.932 – 7.310)   | <0.001       | 5.273 (5.128 – 5.422)        | <0.001       |
| Viral conjunctivitis (B30)        | 0.576          | 1.161 (1.137 – 1.184)   | <0.001       | 1.099 (1.077 – 1.122)        | <0.001       |
| Otitis media (H65 + H66)          | 0.836          | 2.546 (2.492 – 2.602)   | <0.001       | 2.243 (2.194 – 2.292)        | <0.001       |

**Figures**
Figure 1

The probability of confidence (%) and time to onset (days) for the sequence patterns between atopic dermatitis and infectious disorders. The first number in parentheses indicates the probability of confidence (%), and the second number indicates the time to onset (days).