Increased risk of herpes zoster in patients with peptic ulcers

A longitudinal follow-up study using a national sample cohort

Young Ju Jin, MD, PhD<sup>a</sup>, Bumjung Park, MD, PhD<sup>b</sup>, Il-Seok Park, MD, PhD<sup>c</sup>, Hyo Geun Choi, MD, PhD<sup>cd</sup>∗

Abstract
The purpose of this study was to investigate the association of herpes zoster infection with peptic ulcer disease in a Korean population.

The Korean National Health Insurance Service selects samples directly from the entire Korean population database, and 1,125,691 participants with 114,369,638 medical claim codes were selected from the entire Korean population (50 million). A total of 127,802 peptic ulcer disease participants were matched with 127,802 control participants at a ratio of 1:1, considering age group, sex, income group, region of residence, hypertension, diabetes, and dyslipidemia. We analyzed stratified Cox proportional hazard models to calculate the hazard ratios of peptic ulcer with respect to herpes zoster. For subgroup analyses, we divided the participants by age, sex, and time periods after the index date.

The rate of herpes zoster was higher in the peptic ulcer group (9.1% [11,669/127,802]) than in the control group (7.4% [9,397/127,802], P < .001). The adjusted hazard ratio of herpes zoster was 1.24 (95% CI = 1.21–1.28, P < .001). In subgroup analyses performed according to age and sex, all crude and adjusted hazard ratios of herpes zoster were higher in the peptic ulcer disease group than in the control group (each P < .05). In another subgroup analysis according to follow-up periods, the crude and adjusted hazard ratios of herpes zoster were higher in the peptic ulcer disease group than in the control group except for < 1 year periods after the index dates (each P < .001).

The hazard ratios of herpes zoster were significantly increased in the peptic ulcer group compared with those in the control group in all age and sex groups.

Abbreviations: CIs = confidence intervals, HIRA = health insurance review & assessment, HRs = hazard ratios, HZ = herpes zoster, NHIS-NSC = Korean National Health Insurance Service-National Sample Cohort, NSAIDs = Nonsteroidal anti-inflammatory drugs, PUD = peptic ulcer disease, VZV = varicella-zoster virus.

Keywords: herpes zoster, longitudinal follow-up study, peptic ulcers, varicella-zoster virus

1. Introduction

Peptic ulcer disease (PUD) is an acid-peptic injury in the gastric tract, especially the stomach or proximal duodenum. The main symptoms of gastric ulcers are abdominal pain, nausea and vomiting after eating and weight loss. Patients with duodenal ulcers feel hungry and show nocturnal abdominal pain. The annual incidence was reported to be approximately 0.1% to 0.3% in Western countries.[1,2] *Helicobacter pylori* (*H pylori*) infection is the most common cause of PUD (48%), followed by the use of nonsteroidal anti-inflammatory drugs (NSAIDs, 24%) in the USA.[3] In Korea, *H pylori* infection was the most common cause (48%), followed by ulcerogenic drugs, including aspirin, NSAIDs and warfarin (21%).[4] The main complications of PUD in Korea were reported as ulcer bleeding (13.2%), perforation (0.1%) and gastric outlet obstruction (1%).[5] and the mortality rate ranged from 1.7% to 10.7% after bleeding and from 10.7% to 27.0% after perforation.[6] In addition, PUD can cause chronic malnutrition due to bleeding, dysphagia and sleep disorders, which can weaken an individual’s immune system.

Herpes zoster (HZ), known as shingles, is caused by reactivation of varicella-zoster virus (VZV) in the cranial nerve or dorsal root ganglia after primary infection. This reactivation of VZV is associated with decreased cell-mediated immunity as a result of aging or cell-mediated immunosuppression.[7–9] The risk of reactivation has been reported to be increased in women,
nervous system. In the USA, the incidence rate of HZ was increased to 10.7/1000 in patients greater than 80 years old. However, the participants were not matched with respect to ischemic heart disease, cerebral stroke, depression, atopic dermatitis, and chronic obstructive pulmonary disease (COPD) histories because strict matching based on these characteristics increased the drop-out rate for subjects due to a lack of control participants.

2.3. Variables

The age groups were classified using the following 5-year age intervals: 20–24, 25–29, 30–34, and 85+ years old. A total of 14 age groups were designated. The income groups were initially divided into 41 classes (one health aid class, 20 self-employment health insurance classes, and 20 employment health insurance classes). These groups were recategorized into 5 classes (class 1 [lowest income]–5 [highest income]). The region of residence was divided into 16 areas according to administrative district. These regions were regrouped into urban (Seoul, Busan, Daegu, Incheon, Gwangju, Daejeon, and Ulsan) and rural (Gyeonggi, Gangwon, Chungcheongbuk, Chungcheongnam, Jeollabuk, Jeollanam, Gyeongsangbuk, Gyeongsangnam, and Jeju) areas.

The participants’ prior medical histories were evaluated using ICD-10 codes. To ensure an accurate diagnosis, hypertension (I10 and I11), diabetes (E10-E14), and dyslipidemia (E78) were regarded as present if a participant was treated ≥ 2 times. These metabolic diseases were adjusted in that this study had no records of obesity. Ischemic heart disease (I24 and I25) and cerebral stroke (I60-I66) were regarded as present if a participant was treated ≥ 2 times. Depression was defined based on ICD-10 codes from F31 (bipolar affective disorder) to F39 (unspecified mood disorder) recorded by a psychiatrist ≥ 2 times. Atopic dermatitis (L20) was defined as present if a participant was treated ≥ 2 times, as in a previous study. COPD was determined by J43 (emphysema) through J44 (other chronic obstructive pulmonary disease) for individuals who were treated with SABA, LABA, LAMA, and a corticosteroid ≥ 2 times. This designation was adjusted in that this study had no records of smoking.

2.4. Statistical analyses

Chi-square tests were used to compare the general characteristics between the peptic ulcer and control groups. Stratified Cox proportional hazard models were used to assess HRs for peptic ulcers with respect to HZ. In this analysis, crude (simple) and adjusted (for ischemic heart disease, cerebral stroke, depression, atopic dermatitis, and COPD) models were used, and 95% confidence intervals (CIs) were calculated. In these analyses, age, sex, income, region of residence, hypertension, diabetes, and dyslipidemia were stratified. Kaplan-Meier survival analysis and the log-rank test were used (Fig. 2).

For the subgroup analyses, we divided the participants by age (20–39, 40–59, and 60+ years) and sex (men and women).
another subgroup analysis, we calculated HRs for follow-up periods of < 1 year, 2 years, 3 years, 4 years and ≥ 5 years after the index date.

Two-tailed analyses were conducted, and P values less than .05 were considered to indicate significance. The results were statistically analyzed using SPSS v. 21.0 (IBM, Armonk, NY).

3. Results

The time duration from the index date to HZ was 63.3 months (SD = 37.4) in the peptic ulcer group and 63.3 months (SD = 38.3) in the control group. The rate of HZ was higher in the peptic ulcer group (9.1% [11,669/127,802]) than in the control group (7.4% [9,397/127,802], P < .001, Table 1). The general characteristics (age, sex, income, region of residence, and hypertension, diabetes, and dyslipidemia histories) of the participants were the same between the two groups due to the matching procedure (P = .001, Table 1). The general characteristics (age, sex, income, region of residence, and hypertension, diabetes, and dyslipidemia histories) of the participants were the same between the two groups due to the matching procedure (P = 1.000).

The crude and adjusted HRs of HZ were 1.26 (95% CI = 1.22–1.29) and 1.23 (95% CI = 1.20–1.27), respectively, in the peptic ulcer group than in the control group (each P < .001, Table 2).

In subgroup analyses performed according to age and sex, all crude and adjusted HRs of HZ were higher in the peptic ulcer group than in the control group (each P < .001, Table 3). The adjusted HRs were 1.18 (95% CI = 1.06–1.32) in < 40-year-old men; 1.33 (95% CI = 1.21–1.46) in < 40-year-old women; 1.27 (95% CI = 1.19–1.35) in 40 to 59-year-old men; 1.21 (95% CI = 1.15–1.27) in 40–59-year-old women; 1.25 (95% CI = 1.16–1.35) in ≥ 60-year-old men; and 1.20 (95% CI = 1.13–1.28) in ≥ 60-year-old women.

In another subgroup analysis according to follow-up periods, the crude and adjusted HRs of HZ were higher in the peptic ulcer group than in the control group, except for the < 1 year period after the index date (each P < .001, Table 4). The adjusted HRs were 1.31 (95% CI = 1.20–1.44) in the period of 2 years; 1.26 (95% CI = 1.15–1.38) in the period of 3 years; 1.31 (95% CI = 1.20–1.44) in the period of 4 years; and 1.24 (95% CI = 1.20–1.29) in the period of ≥ 5 years.

4. Discussion

In this study, the peptic ulcer group (9.1%) showed an increased rate of HZ compared to that of the control group (7.4%), and the HR of HZ was significantly higher in the peptic ulcer group (HR = 1.26, 95% CI = 1.22–1.29) after matching for age, sex, income, region of residence, and hypertension, diabetes, and dyslipidemia histories. Furthermore, this study showed that PUD was significantly associated with reactivation of HZ (adjusted HR = 1.23, 95% CI = 1.20–1.27) after excluding comorbidities, such as ischemic heart disease, cerebral stroke, depression, atopic dermatitis and COPD histories, which were previously studied as possible causes of HZ.[19–22]

Chen et al., reported an increased HR of HZ in a PUD (adjusted HR = 1.77, 95% CI = 1.64–1.91) group compared to a control group matched for age, gender, year of cohort entry, DM,
cancer and hypertension.\cite{14} Our study showed similar results to those of the Taiwan group. Moreover, this report is the largest study to suggest the positive association HZ in the PUD group compared to that in the control group.

The major risk factors of PUD are *H pylori* infection and the use of NSAIDs or aspirin causing mucosal damage. Initially, *H pylori* usually infects in childhood, and related diseases occur in adults. Although *H pylori* has infected approximately 50% of the global population, most infected individuals (>80%) do not develop any disease and remain asymptomatic throughout their life.\cite{23} This outcome of infection is determined by the inflammatory response, host genetic predisposition and environment.\cite{12,14} *H pylori* strains should be recognized by epithelial innate immune receptors, which stimulate epithelial proinflammatory cytokine release. However, innate immune receptors cannot efficiently recognize *H pylori*, which could contribute to persistent bacterial survival. Chronic stimulation of the innate immune response precipitates the release of antibacterial peptides and immune effector cells, such as phagocytes, complement and natural killer (NK) cells, which play a key role in humoral immunity and cell-mediated immunity.\cite{23} It has been reported that T helper type 1 cells are selectively increased and cause immune-mediated apoptosis of gastric epithelial cells during *H pylori* infection.\cite{24} In this result, PUD patients with peptic ulcers caused by *H pylori* infection, develop impairment of humoral and cell-mediated immunity. NSAIDs and aspirin are major causes of non-*H pylori*-associated PUD. Mainly, these drugs induce PUD by gastric mucosal cell apoptosis and necrosis through direct gastric mucosal injury combined with topical toxicity.\cite{26} Similar to *H pylori*-induced PUD, non-*H pylori*-induced PUD shows impaired innate and adaptive immune defense mechanisms. HZ is caused by reactivation of VZV in the cranial nerve or dorsal root ganglia. The incidence is estimated to be 30%, and it increases to 50% in unvaccinated people who live to 85 years. The virus is maintained in its latent form by VZV-specific cell-mediated immunity. Aging and cell-mediated immunosuppressive disorders are definite risk factors, and female sex, black race, malnutrition, metabolic diseases and social habits are possible risk factors for HZ.\cite{9,10} HZ is characterized by severe painful vesicles following a dermatome, and postherpetic pain can persist many months and years after rash resolution in 10 to 50% of patients with HZ. An increased susceptibility for HZ has been reported in patients with autoimmune diseases, malignancies such as lymphoma and leukemia, human immunodeficiency virus infection, sleep disorders, personal and familial history of HZ, inflammatory bowel disease, psoriasis, psychiatric disease and major depression disease.\cite{10,27–33}

In our study, the HR of HZ was significantly higher in PUD patients than in control individuals. There are possible theories that can explain our result. First, as described above, PUD damages the gastric mucosa, which has goblet cells secreting mucous acting as a physical barrier and dendritic cells working as...
antigen presenting cells acting as initiators of the adaptive immunity cascade. In this scenario, impaired cell-mediated immunity has a key role in VZV reactivation. Second, pain and abdominal discomfort caused by PUD can induce sleep disturbances, dyspepsia and malnutrition, which are known risk factors for VZV reactivation.\(^\text{3,4,5}\) Third, anemia is one of the plausible explanations for the association between PUD and HZ. Chronic anemia increases infection susceptibility because iron has an important role in immune cell proliferation.\(^\text{37,38}\) We could not analyze anemia in this study because we did not have blood test data. However, the main complications of PUD are chronic anemia, dyslipidemia, and NSAIDs or aspirin induced PUD can be recurred easily. Because the patient has to take the causative drug again. The clinical features of PUD like as episodic gnawing abdominal discomfort caused by PUD can induce sleep disturbance, dyspepsia and malnutrition, which are known risk factors for VZV reactivation.\(^\text{3,4,5}\) Third, anemia is one of the

### Table 1

**General Characteristics of Participants.**

| Characteristics | Total participants | Peptic ulcer (n, %) | Control (n, %) | P value |
|-----------------|--------------------|--------------------|---------------|---------|
| Age (years old) |                    |                    |               |         |
| 20–24           | 5,662 (4.6)        | 5,662 (4.6)        | 1.00          |         |
| 25–29           | 8,464 (6.6)        | 8,464 (6.6)        | 1.00          |         |
| 30–34           | 11,391 (8.9)       | 11,391 (8.9)       | 1.00          |         |
| 35–39           | 13,743 (10.8)      | 13,743 (10.8)      | 1.00          |         |
| 40–44           | 16,240 (12.7)      | 16,240 (12.7)      | 1.00          |         |
| 45–49           | 16,583 (13.0)      | 16,583 (13.0)      | 1.00          |         |
| 50–54           | 14,558 (11.4)      | 14,558 (11.4)      | 1.00          |         |
| 55–59           | 12,189 (9.5)       | 12,189 (9.5)       | 1.00          |         |
| 60–64           | 11,324 (8.9)       | 11,324 (8.9)       | 1.00          |         |
| 65–69           | 8,662 (6.8)        | 8,662 (6.8)        | 1.00          |         |
| 70–74           | 5,187 (4.1)        | 5,187 (4.1)        | 1.00          |         |
| 75–79           | 2,462 (1.9)        | 2,462 (1.9)        | 1.00          |         |
| 80–84           | 873 (0.7)          | 873 (0.7)          | 1.00          |         |
| 85+             | 264 (0.2)          | 264 (0.2)          | 1.00          |         |
| Sex             |                    |                    |               |         |
| Male            | 61,968 (48.5)      | 61,968 (48.5)      | 1.00          |         |
| Female          | 65,834 (51.5)      | 65,834 (51.5)      | 1.00          |         |
| Income          |                    |                    |               |         |
| 1 (lowest)      | 18,357 (14.4)      | 18,357 (14.4)      | 1.00          |         |
| 2               | 19,546 (15.3)      | 19,546 (15.3)      | 1.00          |         |
| 3               | 24,054 (18.8)      | 24,054 (18.8)      | 1.00          |         |
| 4               | 30,069 (23.5)      | 30,069 (23.5)      | 1.00          |         |
| 5 (highest)     | 35,776 (28.0)      | 35,776 (28.0)      | 1.00          |         |
| Region of residence |                |                    |               |         |
| Urban           | 57,896 (45.3)      | 57,896 (45.3)      | 1.00          |         |
| Rural           | 69,906 (54.7)      | 69,906 (54.7)      | 1.00          |         |
| Hypertension    | 44,813 (35.1)      | 44,813 (35.1)      | 1.00          |         |
| Diabetes        | 24,342 (19.0)      | 24,342 (19.0)      | 1.00          |         |
| Dyslipidemia    | 38,770 (30.3)      | 38,770 (30.3)      | 1.00          |         |
| Ischemic heart disease | 8,691 (7.0) | 8,691 (7.0)      | <0.001*       |         |
| Cerebral stroke | 13,192 (10.3)      | 11,601 (9.1)       | <0.001*       |         |
| Depression      | 16,153 (12.6)      | 9,755 (7.6)        | <0.001*       |         |
| Atopic dermatitis| 6,107 (4.8)        | 4,743 (3.7)        | <0.001*       |         |
| Chronic obstructive pulmonary disease | 6,978 (5.5) | 4,885 (3.8)      | <0.001*       |         |
| Herpes zoster   | 11,669 (9.1)       | 9,397 (7.4)        | <0.001*       |         |

**Table 2**

**Crude and adjusted hazard ratios (95% confidence interval) of peptic ulcer for herpes zoster.**

| Characteristics | Peptic ulcer Crude P-value Adjusted\(^{1,4}\) P value |
|-----------------|---------------------------------------------|
| Peptic ulcer    | 1.26 (1.22–1.29) <0.001* 1.23 (1.20–1.27) <0.001* |
| Control         | 1.00                                        |

**Table 3**

**Subgroup analysis of crude and adjusted hazard ratios (95% confidence interval) of peptic ulcer for herpes zoster according to age and sex.**

| Characteristics | Crude\(^1\) P-value Adjusted\(^{1,4}\) P value |
|-----------------|---------------------------------------------|
| Age < 40 years old, men (n=37,804) | | |
| Peptic ulcer    | 1.20 (1.07–1.34) .001* 1.19 (1.06–1.32) .003* |
| Control         | 1.00                                        |
| Age < 40 years old, women (n=41,116) | | |
| Peptic ulcer    | 1.36 (1.24–1.49) <0.001* 1.33 (1.21–1.46) <0.001* |
| Control         | 1.00                                        |
| Age 40–59 years old, men (n=59,202) | | |
| Peptic ulcer    | 1.29 (1.22–1.37) <0.001* 1.27 (1.19–1.35) <0.001* |
| Control         | 1.00                                        |
| Age 40–59 years old, women (n=59,938) | | |
| Peptic ulcer    | 1.23 (1.17–1.29) <0.001* 1.21 (1.15–1.27) <0.001* |
| Control         | 1.00                                        |
| Age ≥ 60 years old, men (n=26,930) | | |
| Peptic ulcer    | 1.29 (1.19–1.39) <0.001* 1.25 (1.16–1.35) <0.001* |
| Control         | 1.00                                        |
| Age ≥ 60 years old, women (n=30,614) | | |
| Peptic ulcer    | 1.23 (1.15–1.31) <0.001* 1.20 (1.13–1.28) <0.001* |
| Control         | 1.00                                        |

\(^1\) Cox-proportional hazard regression model. Significance at P < .05.
\(^2\) Stratified model for age, sex, income, region of residence, hypertension, diabetes mellitus, and dyslipidemia histories.
\(^4\) Adjusted model for ischemic heart disease, cerebral stroke, depression, atopic dermatitis, and chronic obstructive pulmonary disease histories.
Table 4

| Characteristics | Crude1 | P value | Adjusted2,4 | P value |
|-----------------|-------|---------|-------------|---------|
| Periods ≤ 1 year |       |         |             |         |
| Peptic ulcer    | 1.06  | .096–1.15 | .171 | 1.04 | .96–1.13 | .377 |
| Control         | 1.00  |         |             |         |
| Periods 2 year  |       |         |             |         |
| Peptic ulcer    | 1.34  | 1.22–1.46 | .001* | 1.31 | 1.20–1.44 | .001* |
| Control         | 1.00  |         |             |         |
| Periods 3 year  |       |         |             |         |
| Peptic ulcer    | 1.28  | 1.17–1.40 | .001* | 1.26 | 1.15–1.38 | .001* |
| Control         | 1.00  |         |             |         |
| Periods 4 year  |       |         |             |         |
| Peptic ulcer    | 1.34  | 1.23–1.46 | .001* | 1.31 | 1.20–1.44 | .001* |
| Control         | 1.00  |         |             |         |
| Periods ≥ 5 years |     |         |             |         |
| Peptic ulcer    | 1.27  | 1.23–3.13 | .001* | 1.24 | 1.20–1.29 | .001* |
| Control         | 1.00  |         |             |         |

1 Cox-proportional hazard regression model. Significance at P < .05.
2 Stratified model for age, sex, income, region of residence, hypertension, diabetes mellitus, and dyslipidemia histories.
3 Adjusted model for ischemic heart disease, cerebral stroke, depression, atopic dermatitis, and chronic obstructive pulmonary disease histories.

This study has several benefits. First, we used participants from a large representative nationwide population who underwent health screening examinations. This report is the largest study to show that PUD is one of the risk factors for HZ. We analyzed the HRs of HZ in a PUD group and compared them to the HRs in a well-matched control group. The control group was randomly selected and matched by age group, sex, income group, region of residence, and medical history (e.g., hypertension, diabetes, and dyslipidemia) to prevent selection bias. Second, this study is the first report on the relationship between PUD and HZ after excluding direct possible reasons for HZ, including ischemic heart disease, cerebral stroke, depression, atopic dermatitis, and COPD, using an adjusted Cox proportional hazard regression model to minimize confounders.

This study has several limitations. First, we used patient claim codes from the HIRA database to diagnose HZ and PUD. Second, we could not evaluate smoking and alcohol habits, diet and obesity, which have an important effect on general health status. However, we considered the metabolic disease history instead of obesity and COPD instead of smoking history. Third, we could not identify whether PUD was treated. Fourth, medication history for NSAIDs or aspirin could not be evaluated because many kinds of these drugs are over-the-counter drugs in Korea.

5. Conclusion

The HR of HZ was significantly increased in the PUD group. After classifying cases into sex and age groups, HZ showed a significantly positive association with PUD.

Acknowledgments

The manuscript was edited for proper English language, grammar, punctuation, spelling, and overall style by the highly qualified native English-speaking editors at American Journal Experts (E288-00CA-4EB3-15B0-EA2P).

References

[1] Lasans A, Chan FK. Peptic ulcer disease. Lancet 2017;390:613–24.
[2] Sun S, Kupers E, El-Serag H. Systematic review: the global incidence and prevalence of peptic ulcer disease. Aliment Pharmacol Therap 2009;29:938–46.
[3] Ramakrishnan K, Salinas RC. Peptic ulcer disease. Am Fam Physician 2007;76:1005–12.
[4] Kim JJ, Kim N, Park HK, et al. Clinical characteristics of patients diagnosed as peptic ulcer disease in the third referral center in 2007. Korean J Gastroenterol 2012;59:338–46.
[5] Jang HJ, Choi MH, Shin WG, et al. Has peptic ulcer disease changed during the past ten years in Korea? A prospective multi-center study. Dig Dis Sci 2008;53:1527–31.
[6] Lau JY, Sung J, Hill C, et al. Systematic review of the epidemiology of complicated peptic ulcer disease: incidence, recurrence, risk factors and mortality. Gastroenterology 2011;8:102–13.
[7] Gershon AA, Gershon MD, Breuer J, et al. Advances in the understanding of the pathogenesis and epidemiology of herpes zoster. J Clin Virol 2010;48:52–7.
[8] Burke BL, Steele RW, Beard OW, et al. Immune responses to varicella-zoster in the aged. Arch Intern Med 1982;142:291–3.
[9] Thomas SL, Hall AJ. What does epidemiology tell us about risk factors for herpes zoster? Lancet Infect Dis 2004;4:26–33.
[10] Cohen JT. Herpes zoster. N Engl J Med 2013;369:255–63.
[11] Kawai K, Yawn BP. Risk factors for herpes zoster: a systematic review and meta-analysis. Mayo Clin Proc 2017.
[12] Yawn BP, Saddier P, Woolan PC, Sauver JLS, Kurland MJ, Sy LS. A population-based study of the incidence and complications of herpes zoster before zoster vaccine introduction. Rochester: Mayo Clinic Proceedings; 2007.
[13] Kim YJ, Lee CN, Lim C-Y, et al. Population-based study of the epidemiology of herpes zoster in Korea. J Korean Med Sci 2014;29:1706–10.
[14] Chen J-Y, Cheng T-J, Chang C-Y, et al. Increased incidence of herpes zoster in adult patients with peptic ulcer disease: a population-based cohort study. Int J Epidemiol 2013;42:1873–81.
[15] Kim SY, Lee JK, Sim S, et al. Hearing impairment increases the risk of distal radius, hip, and spine fractures: A longitudinal follow-up study using a national sample cohort. PLoS One 2018;13.
[16] Kim SY, Sim S, Kim H-J, et al. Sudden sensory neural hearing loss is not predictive of myocardial infarction: A longitudinal follow-up study using a national sample cohort. Sci Rep 2018;8:17–7.
[17] Yu JS, Lee CJ, Lee HS, et al. Prevalence of atopic dermatitis in Korea: analysis by using national statistics. J Kor Med Sci 2012;27:681–5.
[18] The Korean Academy of Tuberculosis and Respiratory Diseases. https://www.lungkorea.org/bbs/?code=guide. Published 2018. Accessed May 15, 2019.
[19] Jones MP. The role of psychosocial factors in peptic ulcer disease: beyond Helicobacter pylori and NSAIDs. J Psychosom Res 2006;60:407–12.
[20] Leventstein S, Kaplan GA, Smith MW. Psychological predictors of peptic ulcer incidence in the Alameda County Study. J Clin Gastroenterol 1997;24:140–6.
[21] Ong PY, Leung DY. Bacterial and viral infections in atopic dermatitis: a comprehensive review. Clin Rev Allergy Immunol 2016;51:329–37.
[22] Joesoef RM, Harpaz R, Leung J, Bialek SR. Chronic medical conditions as risk factors for herpes zoster. Rochester: Mayo Clinic Proceeding; 2012.
[23] Robinson K, Argent RH, Atherton JC. The inflammatory and immune response to Helicobacter pylori infection. Best Pract Res Clin Gastroenterol 2007;21:237–59.
[24] Tsai H-F, Hsu P-N. Interplay between Helicobacter pylori and immune cells in immune pathogenesis of gastric inflammation and mucosal pathology. Cell Mol Immunol 2010;7:255–9.
[25] Abbas AK, Lichtman AH, Pillai S. Cellular and molecular immunology E-book. Amsterdam: Elsevier Health Sciences; 2014.
[26] Tomisato W, Tsutsumi S, Rokutan K, et al. NSAIDs induce both necrosis and apoptosis in guinea pig gastric mucosal cells in primary culture. Am J Physiol Gastrointest Liver Physiol 2001;281:G1092–100.
[27] Yun H, Yang S, Chen L, et al. Risk of herpes zoster in autoimmune and inflammatory diseases: implications for vaccination. Arthritis Rheumatol 2016;68:2328–37.
[28] Chung W-S, Lin H-H, Cheng N-C. The incidence and risk of herpes zoster in patients with sleep disorders: a population-based cohort study. Medicine 2016;95:e2195.
[29] Marim M, Harpaz R, Zhang J, Wollan PC, Bialek SR, Yawn BP. Risk factors for herpes zoster among adults. Oxford University Press; 2016.
[30] Chang K, Lee H-S, Kim Y-J, et al. Increased risk of herpes zoster infection in patients with inflammatory bowel diseases in Korea. Clin Gastroenterol Hepatol 2018;16: 1928–36.e2.
[31] Tsai S-Y, Chen H-J, Lio C-F, et al. Increased risk of herpes zoster in patients with psoriasis: A population-based retrospective cohort study. PloS One 2017;12.
[32] Yang YW, Chen YH, Lin HW. Risk of herpes zoster among patients with psychiatric diseases: a population based study. J Eur Acad Dermatol Venereol 2011;25:447–53.
[33] Irwin M, Costlow C, Williams H, et al. Cellular immunity to varicella-zoster virus in patients with major depression. J Infect Dis 1998;178(Supplement_1):S104–8.
[34] Mahdi BM. Role of immunity in gastric ulcer. J Gastroenterol Hepatol Res 2013;2:803–6.
[35] Banchereau J, Steinman RM. Dendritic cells and the control of immunity. Nature 1998;392:245–52.
[36] Chen J-Y, Chang C-Y, Lin Y-S, et al. Nutritional factors in herpes zoster, postherpetic neuralgia, and zoster vaccination. Popul Health Manag 2012;15:391–7.
[37] Oppenheimer SJ. Iron and its relation to immunity and infectious disease. J Nutr 2001;131:358S–80S.
[38] Beard JL. Iron biology in immune function, muscle metabolism and neuronal functioning. J Nutr 2001;131:568S–80S.
[39] Joynson D, Walker DM, Jacobs A, et al. Defect of cell-mediated immunity in patients with iron-deficiency anaemia. Lancet 1972;300:1058–9.