No Increased Risk of Herpes Zoster Found in Cirrhotic Patients: A Nationwide Population-Based Study in Taiwan

Ping-Hsun Wu1,3, Yi-Ting Lin2, Chun-Nan Kuo4,5, Wei-Chiao Chang4,5, Wei-Pin Chang6

1 Division of Nephrology, Department of Internal Medicine, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan, 2 Department of Family Medicine, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan, 3 Graduate Institute of Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan, 4 Department of Pharmacy, Taipei Medical University-Wanfang Hospital, Taipei, Taiwan, 5 Department of Clinical Pharmacy, School of Pharmacy, Taipei Medical University, Taipei, Taiwan, 6 Department of Healthcare Management, Yuanpei University, Hsinchu, Taiwan

Abstract

Background: The association between liver cirrhosis (LC) and herpes zoster has rarely been studied. We investigated the hypothesis that LC, known as an immunodeficiency disease, may increase the risk of herpes zoster using a national health insurance database in Taiwan.

Materials and Methods: The study cohort included cirrhotic patients between 1998 and 2005 (n = 4667), and a ratio of 1:5 randomly sampled age- and gender-matched control patients (n = 23,335). All subjects were followed up for 5 years from the date of cohort entry to identify whether or not they had developed herpes zoster. Cox proportional-hazard regressions were performed to evaluate 5-year herpes zoster-free survival rates.

Results: Of all patients, 523 patients developed herpes zoster during the 5-year follow-up period, among whom 82 were LC patients and 441 were in the comparison cohort. The adjusted hazard ratio (AHR) of herpes zoster in patients with LC was not higher (AHR: 0.77, 95% confidence interval: 0.59–1.01, p = 0.06) than that of the controls during the 5-year follow-up. No increased risk of herpes zoster was found in LC patients after stratification by age, gender, urbanization level, income, geographic region, and all comorbidities.

Conclusions: This large nationwide population-based cohort study suggests that there is no increased risk for herpes zoster among people who have LC compared to a matching population.

Introduction

Herpes zoster is caused by spontaneous reactivation of a latent varicella-zoster virus (VZV) that resides in sensory ganglia and dorsal nerve roots following a varicella infection [1]. The disease usually manifests as painful vesicular skin lesions, which are limited to 1 to 3 dermatomes, and related neurological disorders. Several neurologic complications may be found, including post-herpetic neuralgia, ventriculitis, vasculopathy, cranial nerve palsies, encephalitis, and myelitis [2]. The most common complication is post-herpetic neuralgia, which results in functional disability and a poor quality of life. In addition, epidemiologic studies also demonstrated the risk of stroke or cancer increases among patients who suffer from herpes zoster [3–6]. Therefore, herpes zoster has great impacts on the health of adults and health systems. The incidence and severity increase after the age of 50 years [7–10]. The incidence of herpes zoster is 1.2–4.9 cases per 1000 person-years in the general population [10–12]. Old age [13], diabetes mellitus (DM) [14], chronic renal failure (CRF) [15,16], and chronic obstructive pulmonary disease (COPD) [17] are established risk factors for herpes zoster. Herpes zoster risk also increases with immunocompromised diseases, such as human immunodeficiency virus (HIV) infection [18,19], systemic lupus erythematosus (SLE) [20], and rheumatoid arthritis (RA) [21–23], as well as transplant recipients [24]. Although the mechanism of reactivation of latent VZV remains unclear, decreasing cellular immunity to VZV predisposes one to the recurrence of herpes zoster [25,26].

Patients who develop liver cirrhosis (LC) exhibit acquired immune dysfunction because of poor homeostasis and malnutrition. Most of the host defense systems are compromised in cirrhotic patients, including antigen-specific and nonspecific functions, clearance capacities of the reticuloendothelial system, and macrophage, neutrophil, and lymphocyte functions [27]. Monocyte spread, chemotaxis, bacterial phagocytosis, and bacterial killing significantly deteriorate in cirrhotic patients [28]. Bacterial and fungal infections are more common and virulent in patients with cirrhosis than in the overall population [29]. In
addition, LC can also be considered a risk of viral infection, such as cytomegalovirus [29,30]. It is reasonable to hypothesize that the immune dysregulation found in LC may put patients at a higher risk of developing herpes zoster. However, data are limited regarding the risk of herpes zoster among patients with LC. The goal of our study was to investigate whether patients with LC have a higher incidence of herpes zoster than the general population. This study provides unique data based on the Longitudinal Health Insurance Database (LHID).

**Methods**

**Database**

National Health Insurance (NHI) is a mandatory health insurance program in Taiwan that provided comprehensive coverage for medical care up to 99% of the population in 2009. Because NHI is a single-payer compulsory program that covers all forms of health care for residents in Taiwan, the NHIRD comprehensively includes claim data on both outpatient and inpatient services for nearly the entire 23.7 million population of this country. All claims data are collected in the NHI Research Database (NHIRD) and are managed by the Taiwan National Health Research Institutes (NHRI). Data files in the NHIRD include all ambulatory claims, inpatient claims, details of ambulatory care and inpatient orders, and prescriptions dispensed at contracted pharmacies. Data used to perform the analyses conducted in this study were retrieved from the LHID 2005 (LHID2005), a subset of the NHIRD. The LHID2005 consists of all the original medical claims for 1,000,000 enrollees’ historical ambulatory data and inpatient care data under the Taiwan NHI program from 1997 to 2010, and the database was created and is publicly released to researchers. The NHRI reported that there were no statistically significant differences in age or gender between the randomly sampled group and all beneficiaries of the NHI program. To maintain claims data accuracy, the NHI’s routine practice of performing cross-checks and validations of medical claims ensures the accuracy of the NHIRD diagnostic coding. Because we used de-identified secondary data released to the public for research purposes, our study was exempt from full review by the Institutional Review Board after consultation with the Director of the Kaohsiung Medical University Institutional Review Board.

**Study Population**

We used a study cohort and a comparison cohort to examine the relationship between LC and herpes zoster. We identified 4667 first-time hospitalizations with a discharge diagnosis of LC or patients who had at least two ambulatory care visits for LC (International Classification of Disease, 9th Revision, Clinical Modification (ICD-9-CM) codes 571.2, 571.5, 571.6) between January 1998 and December 2005. The date of the initial diagnosis of LC was assigned as the index date for each LC patient. To improve data accuracy, the LC selection criteria required that all cases with the ICD-9 code be assigned by an internist. We also established selection criteria for herpes zoster patient. We only included herpes zoster cases in this study if they received ≥2 herpes zoster diagnoses for ambulatory care visit or ≥1 diagnose for inpatient care, and the ICD-9 code was assigned by a dermatologist.

Our study used a study cohort and comparison cohort to examine the relationship between LC and herpes zoster. Each LC cohort patient was matched based on age, gender, and index year to five randomly identified beneficiaries without LC to build the comparison cohort. Patients diagnosed with herpes zoster (ICD-9-CM codes 053–053.9) before index date were excluded from both cohorts. We also identified relevant comorbidities, including hypertension (ICD-9-CM codes 401–405), DM (ICD-9-CM codes 250), hyperlipidemia (ICD-9-CM codes 272), HIV (ICD-9-CM codes 042), hepatitis B (ICD-9-CM codes 070.2, 070.3, V02.61), hepatitis C (ICD-9-CM codes 070.41, 070.44, 070.51, 070.54, V02.62), organ transplantation (ICD-9-CM codes 996, V042), chronic renal failure (ICD-9-CM codes 585), SLE (ICD-9-CM codes 710), RA (ICD-9-CM 714), COPD (ICD-9-CM 491, 492, 496), cancer (ICD-9-CM codes 140–208), and alcoholism-associ-
Table 1. Demographic characteristics of selected patients, stratified by the presence/absence of liver cirrhosis in 1998–2005 (n = 28,002).

|                           | Patients with liver cirrhosis (n = 4667) | Patients without liver cirrhosis (n = 23,335) | p value |
|---------------------------|------------------------------------------|-------------------------------------------------|---------|
|                           | n | %   | n | %   |        |
| **Gender**                |   |      |   |      |        |
| Male                      | 3236 | 69.3 | 16,180 | 69.3 |        |
| Female                    | 1431 | 30.7 | 7155 | 30.7 |        |
| **Age (years)**           |   |      |   |      |        |
| 18–39                     | 797 | 17.1 | 3985 | 17.1 |        |
| 40–49                     | 1046 | 22.4 | 5230 | 22.4 |        |
| 50–59                     | 1016 | 21.8 | 5080 | 21.8 |        |
| 60–69                     | 938 | 20.1 | 4690 | 20.1 |        |
| ≥70                       | 870 | 18.6 | 4350 | 18.6 |        |
| **Follow-up, year, mean (SD)** |   | 4.95 | 4.96 | 0.22 |        |
|                           |    | 0.43 | 0.38 |      |        |
| **Urbanization level**    |   |      |   |      | <0.001|
| 1 (most urbanized)        | 1112 | 23.8 | 7483 | 32.1 |        |
| 2                         | 1326 | 28.4 | 6397 | 27.4 |        |
| 3                         | 765 | 16.4 | 3744 | 16.0 |        |
| 4 (least urbanized)       | 1464 | 31.4 | 5711 | 24.5 |        |
| **Monthly income**        |   |      |   |      | <0.001|
| 0                         | 1063 | 22.8 | 4890 | 21.0 |        |
| NT$ 1–15,840              | 862 | 18.5 | 3405 | 14.6 |        |
| NT$ 15,841–25,000         | 2003 | 42.9 | 9515 | 40.8 |        |
| ≥ NT$ 25,001              | 739 | 15.8 | 5525 | 23.7 |        |
| **Geographic region**     |   |      |   |      | <0.001|
| Northern                  | 1787 | 38.3 | 10,942 | 46.9 |        |
| Central                   | 1435 | 30.7 | 5802 | 24.9 |        |
| Southern                  | 1124 | 24.1 | 5406 | 23.2 |        |
| Eastern                   | 321 | 6.9 | 1185 | 5.1 |        |
| **Hypertension**          |   |      |   |      | <0.001|
| Yes                       | 2804 | 60.1 | 12,930 | 55.4 |        |
| No                        | 1863 | 39.9 | 10,405 | 44.6 |        |
| **Hyperlipidemia**        |   |      |   |      | 0.67   |
| Yes                       | 2004 | 42.9 | 10,100 | 43.3 |        |
| No                        | 2663 | 57.1 | 13,235 | 56.7 |        |
| **Diabetes**              |   |      |   |      | <0.001|
| Yes                       | 2168 | 46.5 | 7376 | 31.6 |        |
| No                        | 2499 | 53.5 | 15,959 | 68.4 |        |
| **HIV**                   |   |      |   |      | 0.02   |
| Yes                       | 9 | 0.2 | 27 | 0.1 |        |
| No                        | 4658 | 99.8 | 23,308 | 99.9 |        |
| **Organ transplantation** |   |      |   |      | <0.001|
| Yes                       | 239 | 5.1 | 642 | 2.8 |        |
| No                        | 4428 | 94.9 | 22693 | 97.2 |        |
| **Hepatitis B**           |   |      |   |      | <0.001|
| Yes                       | 1865 | 40.0 | 2653 | 11.4 |        |
| No                        | 2802 | 60.0 | 20,682 | 88.6 |        |
| **Hepatitis C**           |   |      |   |      | <0.001|
| Yes                       | 1375 | 29.5 | 1114 | 4.8 |        |
| No                        | 3292 | 70.5 | 22,221 | 95.2 |        |
ated disorders (ICD-9-CM codes 291, 303, 305.0, 357.5, 425.5, 571.0, 571.1, 571.2, 571.3, 980.0, V11.3).

Level of Urbanization
For the urbanization level in our study, all 365 townships in Taiwan were stratified into 4 levels according to standards established by the Taiwanese NHRI based on a cluster analysis of the 2000 Taiwan census data, with 1 referring to the most urbanized area and 4 referring to the least urbanized. The criteria on which these strata were determined included the population density (persons/km²), the number of physicians per 100,000 people, the percentage of people with a college education, the percentage of people over 65 years of age, and the percentage of agricultural workers.

Statistical Analysis
All data processing and statistical analyses were performed with the Statistical Package for Social Science (SPSS) software, vers. 18.0 (SPSS, Chicago, IL, USA) and SAS vers. 8.2 (SAS System for Windows, SAS Institute, Cary, NC, USA). Pearson $\chi^2$ tests were used to compare differences in geographic location, monthly income, and urbanization level of patients’ residences between the study and comparison groups. We also performed a survival analysis using the Kaplan-Meier method, and used the log-rank test to compare survival distributions between cohorts. The survival period was calculated for patients who suffered from LC until an occurrence of hospitalization, an ambulatory visit for herpes zoster, or the end of the study period (December 31, 2010), whichever came first. After adjusting for urbanization level, monthly income, region, and comorbidities as potential confounders, we performed a Cox proportional-hazards analysis stratified by gender, age group, and index year to examine the risk of herpes zoster during the 5-year follow-up in both cohorts. We further classified the duration of follow up period in both groups. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated to quantify the risk of herpes zoster. The results of comparisons with a two-sided $p$ value of $<0.05$ were considered to represent statistically significant differences.

Ethical Approval
Insurance reimbursement claims data used in this study were from Taiwan’s NHIRD, which is available for research purposes. This study was conducted in accordance with the Helsinki Declaration. This study was also evaluated and approved by the Kaohsiung Medical University’s Institutional Review Board (KMUH-IRB-EXEMPT-20130059).

Results
The research design of this study is shown in Figure 1. The LC cohort contained 4667 patients, and 23,335 patients were included in the comparison cohort. Distributions of demographic characteristics and comorbidities for the LC and comparison cohorts are shown in Table 1. Hypertension ($p<0.001$), DM ($p<0.001$), organ transplantation ($p<0.001$), hepatitis B ($p<0.001$), hepatitis C ($p<0.001$), CRF ($p<0.001$), SLE ($p<0.001$), RA ($p=0.004$), COPD ($p<0.001$), cancer ($p<0.001$), and alcoholism ($p<0.001$) were more prevalent in the LC cohort than the comparison cohort. We also found that cases had a greater tendency to have a lower monthly income ($p<0.001$), to reside in central, southern and eastern Taiwan, and to reside in less-urbanized communities ($p<0.001$) compared to controls.
There were 523 patients diagnosed with herpes zoster during the 5-year follow-up, including 82 LC patients (1.8%) and 441 patients in the comparison cohort (1.9%). The Kaplan-Meier survival curves are shown in Figure 2. The curves demonstrate no significant difference in herpes zoster-free survival rates between the LC and comparison cohorts (log-rank test \( p = 0.55 \)).

The Cox regression analysis showed that the crude HR for herpes zoster did not significantly differ between the LC and comparison cohorts (crude HR: 0.77, 95% CI: 0.59–1.01, \( p = 0.55 \)). After adjusting for potential confounders, our results still showed no statistically different in the risk of herpes zoster (adjusted HR (AHR): 0.77, 95% CI: 0.59–1.01, \( p = 0.06 \)) between LC and non-LC patients (Table 2).

We further investigated whether LC is a time-dependent risk factor for herpes zoster and divided LC patients into 3 groups according to the follow-up period. For the three different follow-up periods, there was still no statistical significance between the case and comparison groups. The 1 and 3-year follow-up period demonstrated no statistical significance (AHR: 1.16; 95% CI: 0.67–2.00, \( p = 0.60 \); AHR: 0.83; 95% CI: 0.59–1.17, \( p = 0.28 \)) (Table 3). We also further conducted a multivariate stratified analysis, and results revealed that LC was not associated with a risk of herpes zoster in any subgroup (Figure 3).

**Discussion**

Our study presents fundamental epidemiological data regarding herpes zoster among patients with LC. To our knowledge, this is the first cohort study to assess the link between LC and the risk of developing herpes zoster. While the validity of ICD-9-CM codes is known to vary widely, an ICD-9-CM diagnosis of herpes zoster and diagnosis by chart review in the Veterans Affairs health care system were in excellent agreement (\( k = 0.92 \)) [23]. We found that 1.8% of patients developed herpes zoster in the 5 years following

**Table 2.** Hazard ratios (HRs) and 95% confidence intervals (CIs) of herpes zoster among liver cirrhosis patients during the 5-year follow-up period from the index ambulatory visit or inpatient care in 1998–2005.

| Development of herpes zoster | Total | Patients with liver cirrhosis | Patients without liver cirrhosis |
|-----------------------------|-------|------------------------------|---------------------------------|
|                             | No.   | (%)                          | No.                             | No.                             |
| 5-year follow-up period     |       |                              |                                 |                                 |
| Yes                         | 523   | 1.9                          | 82                              | 441                             |
| No                          | 27,479| 98.1                         | 4585                            | 22,894                          |
| Crude HR (95% CI)           | 0.93  | (0.74–1.18)                  | 1                               |
| Adjusted HR (95% CI)        | 0.77  | (0.59–1.01)                  | 1                               |

Adjustments are made for patients’ gender, age, urbanization level, geographic region, monthly income, hypertension, diabetes, human immunodeficiency virus, organ transplantation, hepatitis B, hepatitis C, chronic renal failure, systemic lupus erythematosus, rheumatoid arthritis, chronic obstructive pulmonary disease, cancer, and alcoholism.

doi:10.1371/journal.pone.0093443.t002
an LC diagnosis. Our nationwide population-based study clearly demonstrated that after adjusting for potential confounders, patients with LC were not at an increased risk of herpes zoster. A further multivariate stratified analysis and different follow-up time analysis still showed no increased risk of herpes zoster among patients with LC.

Patients with suppressed cell-mediated immunity caused by immunosuppressive disorders or therapies, such as elderly people, patients with autoimmune disease, malignancy, or diabetes, are well known to have a higher risk of developing herpes zoster [13,14,21–23,31–33]. Although the mechanism involved in reactivation of latent VZV remains unclear, there is evidence that a decline in cellular immunity to VZV predisposes one to the occurrence of herpes zoster [25,26]. LC, which is related to lymphocyte and macrophage dysfunction and decreased production of proinflammatory cytokines, such as interferon-γ and tumor necrosis factor-α, may be linked to an increased virus infection risk [28]. The liver contains 90% of cells of the reticuloendothelial system (Kupffer cells and sinusoidal endothelial cells), which are essential for pathogen eradication. Monocyte spread, chemotaxis,
and pathogen phagocytosis and killing significantly deteriorate in cirrhosis patients [34]. The phenomena of decreased neutrophil mobilization and phagocytic activity were correlated with the severity of liver disease [35]. Decreased phagocytic activity and the characteristic neutropenia, hyperammonemia, and hyponatremia are exacerbated by shortened neutrophil survival and a decreased opsonization capacity [36,37]. LC is known as innate immunity dysfunction and increased infection risk by bacteria and fungi, and even the cytomegalovirus. In contrast, our cohort study did not show an association between LC and herpes zoster.

From post liver transplantation study, the herpes zoster risk was inconclusive [38,39] and most believe immunosuppressive agents are more important than transplant per se. Besides, in Bajaj et al.’s study, most infection in liver cirrhosis patients were urinary tract infection, spontaneous bacterial peritonitis, spontaneous bacteremia and cellulitis [40]. Herpes zoster was not in the finding in the study. Our result showed the incidence in liver cirrhosis patient was not higher than control group. It was consisted with Bajaj et al.’s study. In McDonald et al.’s study, they found liver disease was not a risk factor for herpes zoster [23]. Although the immunity in liver cirrhosis patients is worse than healthy, other mechanism for virus reactivation may exist.

The present study has a number of strengths. First, this is a large-scale follow-up study using the well-established nationwide NHIRD database. The study cohort is highly representative of the general Taiwanese population. The ascertainment of LC diagnosis and hospitalization and medical comorbidities is likely complete and accurate because the NHIRD has acceptable quality and accuracy of disease coding for epidemiological analyses. Second, patients with hepatitis B, chronic renal failure, human immunodeficiency virus, and alcoholism.

Table 3. Hazard ratios (HRs) and 95% confidence intervals (CIs) of herpes zoster among liver cirrhosis patients during the 1-, 3-, and 5-year follow-up periods from the index ambulatory visit or inpatient care in 1998–2005.

| Development of herpes zoster | 1-year follow-up period | 3-year follow-up period | 5-year follow-up period |
|-----------------------------|-------------------------|-------------------------|-------------------------|
|                             | Patients with liver cirrhosis | Comparison cohort | Patients with liver cirrhosis | Comparison cohort | Patients with liver cirrhosis | Comparison cohort |
| Yes (%)                     | 21 (0.4)                 | 83 (0.4)                | 53 (1.1)                 | 252 (1.1)          | 82 (1.8)                 | 441 (1.9)         |
| No (%)                      | 4646 (99.6)              | 23252 (99.6)            | 4614 (98.9)              | 23,083 (98.9)      | 4585 (98.2)              | 22,894 (98.1)     |
| Crude HR (95% CI)           | 1.27 (0.79–2.05)         | 1                      | 1.05 (0.78–1.42)         | 1                  | 0.93 (0.74–1.18)         | 1                  |
| Adjusted HR (95% CI)        | 1.16 (0.67–2.00)         | 1                      | 0.83 (0.59–1.17)         | 1                  | 0.77 (0.59–1.01)         | 1                  |

Adjustments were made for patients’ gender, age, urbanization level, geographic region, monthly income, hypertension, diabetes, human immunodeficiency virus, organ transplantation, hepatitis B, hepatitis C, chronic renal failure, systemic lupus erythematosus, rheumatoid arthritis, chronic obstructive pulmonary disease, cancer, and alcoholism.

doi:10.1371/journal.pone.0093443.t003

Patients and reviews medical records every year to confirm the validity of the diagnoses and quality of care by randomly sampling a certain percentage of claims from every hospital. It is generally believed that the NHIRD has acceptable quality and accuracy of disease coding for epidemiological analyses. Second, some patients with herpes zoster might have been missed in our database if they did not seek medical help, particularly if their symptoms were mild. Misdiagnosing and misclassification could occur as potential biases. However, utilization of medical services in Taiwan is generally high because there are very low financial barriers to medical care with a very low copayment system. Patients are responsible for a copayment of only US$3~15 each visit, so most patients with herpes zoster would seek medical attention after disease onset. Thus, the number of herpes zoster cases not included in NHIRD is likely to be small [3]. Third, the claims database lacks information on cigarette smoking, alcohol consumption, dietary habits, physical activities, environmental exposure, nutritional status, and family history, which may confound our findings. Fourth, LC is a highly lethal disease in the advanced stage. Therefore, death occurring prior to herpes zoster being diagnosed was considered a competing risk event. However, the death condition cannot be known from NHIRD, which may have biased our results. Fifth, the patients who had herpes zoster after the study period cannot be known from the database. It may be a bias for our result.

In summary, our study provides fundamental epidemiological data that the incidence of herpes zoster is not higher in LC patient in a nationally representative cohort followed-up for 5 years. Studies to find the mechanism for virus reactivation beyond immune insufficiency might be necessary.

Acknowledgments

This study was based in part on data from the NHIRD provided by the Bureau of National Health Insurance, Department of Health, and managed by the National Health Research Institutes. The interpretation and conclusions contained herein do not represent the views of the Bureau of National Health Insurance, Department of Health or National Health Research Institutes.

Author Contributions

Conceived and designed the experiments: PHW YTL WCC WPC. Performed the experiments: PHW WPC. Analyzed the data: WPC. Contributed reagents/materials/analysis tools: WPC. Wrote the paper: PHW YTL CNK WCC WPC.

Liver Cirrhosis and Herpes Zoster
References

1. Jih JS, Chen YJ, Lin MW, Chen YC, Chen TJ, et al. (2009) Epidemiological features and costs of herpes zoster in Taiwan: a national study 2000 to 2006. Acta Derm Venereol 89: 612–616.

2. Gilden DH, Kleinenschmidt-DeMasters BK, LaGuardia JJ, Mahalingam R, Cohrs RJ (2000) Neurologic complications of the reactivation of varicella-zoster virus. N Engl J Med 342: 635–645.

3. Lin HC, Chien CW, Ho JD (2010) Herpes zoster ophthalmicus and the risk of stroke: a population-based follow-up study. Neurology 74: 792–797.

4. Kang JH, Ho JD, Chen YH, Lin HC (2009) Increased risk of stroke after a herpetic zoster attack: a population-based follow-up study. Stroke 40: 3443–3448.

5. Ho JD, Xirasagar S, Lin HC (2011) Increased risk of a cancer diagnosis after herpetic zoster ophthalmicus: a nationwide population-based study. Ophthalmo-log 118: 1076–1081.

6. Chiu HF, Chen BK, Yang CY (2013) Herpes zoster and subsequent risk of cancer: a population-based study. J Epidemiol 23: 205–210.

7. Wareham DW, Breuer J (2007) Herpes zoster. BMJ 334: 1211–1215.

8. Chiu HF, Chen BK, Yang CY (2013) Herpes zoster and subsequent risk of cancer: a population-based study. J Epidemiol 23: 531–536.

9. Brisson M, Edmunds WJ, Law B, Gay NJ, Wallid R, et al. (2001) Epidemiology of varicella-zoster virus infection in Canada and the United Kingdom. Epidemiol Infect 127: 205–314.

10. Lin YH, Huang LM, Chang IS, Tsai FY, Lu CY, et al. (2010) Disease burden and epidemiology of herpes zoster in pre-vaccine Taiwan. Vaccine 28: 1217–1220.

11. Donahue JG, Choo PW, Manson JE, Platt R (1995) The incidence of herpes zoster. Arch Intern Med 155: 1603–1609.

12. Yawn BP, Saddier P, Wollan PC, St Sauver JL, Kurland MJ, et al. (2007) A population-based study of the incidence and complication rates of herpes zoster before zoster vaccine introduction. Mayo Clin Proc 82: 1341–1349.

13. Schnader K, George LK, Burchett BM, Peper CF (1998) Racial and psychosocial risk factors for herpes zoster in the elderly. J Infect Dis 178 Suppl 1: S67–70.

14. Heymann AD, Chiodick G, Karpati T, Kamer L, Kremer E, et al. (2000) Diabetes as a risk factor for herpes zoster infection: results of a population-based study in Israel. N Engl J Med 342: 226–230.

15. Wu MY, Hsu YH, Su CL, Lin YF, Lin HW (2012) Risk of herpes zoster in CKD: a matched-cohort study based on administrative data. Am J Kidney Dis 60: 548–552.

16. Kuo CC, Lee CT, Lee IM, Ho SC, Yang CY (2012) Risk of herpes zoster in patients treated with long-term hemodialysis: a matched cohort study. Am J Kidney Dis 59: 428–433.

17. Yang YW, Chen YH, Wang KH, Wang CY, Lin HW (2011) Risk of herpes zoster among patients with chronic obstructive pulmonary disease: a population-based study. CMAJ 183: E275–280.

18. Morgan D, Mehe C, Malamba S, Okongo M, Mayanja B, et al. (2001) Herpes zoster and HIV-1 infection in a rural Ugandan cohort. AIDS 15: 223–229.

19. Allergro MB, Dorruci M, Pazzetti P, Rezza G, Sinacori A, et al. (1996) Herpes zoster and progression to AIDS in a cohort of individuals who seroconverted to human immunodeficiency virus. Italian HIV Seroconversion Study. Clin Infect Dis 23: 990–993.

20. Nagasawa K, Yamazaki Y, Tada Y, Kusaba T, Niho Y, et al. (1990) High incidence of herpes zoster in patients with systemic lupus erythematosus: an immunological analysis. Ann Rheum Dis 49: 630–633.

21. Smitten AL, Choi HK, Hochberg MC, Suisa S, Simon TA, et al. (2007) The risk of herpes zoster in patients with rheumatoid arthritis in the United States and the United Kingdom. Arthritis Rheum 57: 1431–1438.

22. Wolfe F, Michael K, Chakravarty EF (2006) Rates and predictors of herpes zoster in patients with rheumatoid arthritis and non-inflammatory musculoskel-etal disorders. Rheumatology (Oxford) 45: 1370–1375.

23. McDonald JR, Zeringue AL, Caplan L, Kangarlanathan P, Xian H, et al. (2009) Herpes zoster risk factors in a national cohort of veterans with rheumatoid arthritis. Clin Infect Dis 48: 1364–1371.

24. Gourishankar S, McCormick JG, Jianggi GS, Preiksaitis JK (2004) Herpes zoster infection following solid organ transplantation: incidence, risk factors and outcomes in the current immunosuppressive era. Am J Transplant 4: 108–115.

25. Hope-Simpson RE (1965) The Nature of Herpes Zoster: A Long-Term Study and a New Hypothesis. Proc R Soc Med 58: 9–20.

26. Levin MJ, Smith JG, Kaulhold RM, Barber D, Hayward AR, et al. (2003) Decline in varicella-zoster virus (VZV)-specific cell-mediated immunity with increasing age and boosting with a high-dose VZV vaccine. J Infect Dis 188: 1356–1344.

27. Bahr MJ, Manns MP (2001) [Function of the immune system in liver cirrhosis]. Z Gastroenterol 39: 601–607.

28. Bonnel AR, Bunchornvavakul C, Reddy KR (2011) Immune dysfunction and infections in patients with cirrhosis. Clin Gastroenterol Hepatol 9: 727–730.

29. Varani S, Lazzaretto T, Margotti M, Masl L, Gramanzieri L, et al. (2000) Laboratory signs of acute or recent cytomegalovirus infection are common in cirrhosis of the liver. J Med Virol 62: 25–28.

30. Tanaka S, Toh Y, Minagawa H, Mori R, Sugimachi K, et al. (1992) Reactivation of cytomegalovirus in patients with cirrhosis: analysis of 122 cases. Hepatology 16: 1409–1414.

31. Thomas SL, Hall AJ (2004) What does epidemiology tell us about risk factors for herpes zoster? Lancet Infect Dis 4: 26–33.

32. Wung PK, Hoefnagk JT, Hoffinan GS, Tibbs AK, Specks U, et al. (2005) Herpes zoster in immunocompromised patients: incidence, timing, and risk factors. Am J Med 118: 1416.

33. Chen HH, Chen YM, Chen TJ, Lan JL, Lin CH, et al. (2011) Risk of herpes zoster in patients with systemic lupus erythematosus: a three-year follow-up study using a nationwide population-based cohort. Clinics (Sao Paulo) 66: 1177–1182.

34. Ghassemi S, Garcia-Tao G (2007) Prevention and treatment of infections in patients with cirrhosis. Best Pract Res Clin Gastroenterol 21: 77–93.

35. Christou L, Pappas G, Falagas ME (2007) Bacterial infection-related morbidity and mortality in cirrhosis. Am J Gastroenterol 102: 1510–1517.

36. Kusaba N, Kunashiro R, Ogata H, Sata M, Tanaka K (1998) In vitro study of neutrophil apoptosis in liver cirrhosis. Intern Med 37: 11–17.

37. Feliu E, Gougerot MA, Hakim J, Cramer E, Auclair C, et al. (1977) Blood laboratory signs of acute or recent cytomegalovirus infection are common in cirrhosis of the liver. J Med Virol 2: 315–323.

38. Christou L, Pappas G, Falagas ME (2007) Bacterial infection-related morbidity and mortality in cirrhosis. Am J Gastroenterol 102: 1510–1517.

39. Kusaba N, Kunashiro R, Ogata H, Sata M, Tanaka K (1998) In vitro study of neutrophil apoptosis in liver cirrhosis. Intern Med 37: 11–17.

40. Bahr MJ, Manns MP (2001) [Function of the immune system in liver cirrhosis]. Z Gastroenterol 39: 601–607.