Meta-Analysis of Observational Studies in Epidemiology

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The incidence rate of herpes zoster in inflammatory bowel disease

A meta-analysis of cohort studies

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Abstract

Inflammatory bowel disease is associated with an increased risk of opportunistic infections. This study aimed to investigate the incidence rate of herpes zoster in patients with inflammatory bowel disease.

A meta-analysis was conducted by searching PubMed literature published from January 2000 to July 2019. The main outcome was the incidence rate of a new diagnosis of herpes zoster in patients previously diagnosed with inflammatory bowel disease. The incidence rate ratio (IRR) and 95% confidence interval (95% CI) for herpes zoster associated with inflammatory bowel disease was measured.

A total of 6 eligible cohort studies matching the entry criteria were included in the meta-analysis, providing 216,552 participants with inflammatory bowel disease and 790 events of herpes zoster among these participants with inflammatory bowel disease. The pooled incidence rate of developing herpes zoster was 10.41 per 1000 person-years in the inflammatory bowel disease group and 6.10 per 1000 person-years in the non-inflammatory bowel disease group, respectively. The meta-analysis demonstrated that patients with inflammatory bowel disease were associated with 1.68-fold increased risk of developing herpes zoster when compared to those without inflammatory bowel disease (IRR = 1.68, 95% CI = 1.53–1.84). Crohn disease and ulcerative colitis were associated with an increased risk of developing herpes zoster (IRR = 1.67, 95% CI = 1.40–1.98 for Crohn disease and IRR = 1.49, 95% CI = 1.34–1.65 for ulcerative colitis, respectively).

Patients with inflammatory bowel disease are at increased risk of developing herpes zoster. We suggest that the vaccination should be considered at the time of inflammatory bowel disease being diagnosed.

Abbreviations: 95% CI = 95% confidence interval, IRR = incidence rate ratio.

Keywords: herpes zoster, inflammatory bowel disease, meta-analysis, vaccination

1. Introduction

Herpes zoster develops when the latent varicella-zoster virus in human dorsal root ganglia is reactivated as the host's immune functions decline.[1–3] The debilitating complication of herpes zoster is the pain caused by acute status of herpes zoster and postherpetic neuralgia.[1–3] Conditions which are associated with the impairment of the host's immunity to varicella-zoster virus are recognized as the risk factors for herpes zoster, including autoimmune diseases, asthma, diabetes mellitus, chronic pancreatitis, corticosteroids therapy, age over 50, and others.[4–7]

Inflammatory bowel disease is a chronic inflammation in the digestive system.

Editor: Nikolay Efimov.

This study was supported in part by Taiwan Ministry of Health and Welfare Clinical Trial Center (MOHW109-TDU-B-212-114004), China Medical University Hospital in Taiwan (DMR109-098), and MOST Clinical Trial Consortium for Stroke (MOST 108-2321-B-039-003). These funding agencies did not influence the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

The authors have no conflicts of interest to disclose.

Supplemental Digital Content is available for this article.

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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How to cite this article: Lai SW, Liao KF, Lin CL, Kuo YH, Liu CS, Hwang BF. The incidence rate of herpes zoster in inflammatory bowel disease: a meta-analysis of cohort studies. Medicine 2021;100:33(e26863).

Received: 20 January 2021 / Received in final form: 15 July 2021 / Accepted: 21 July 2021

http://dx.doi.org/10.1097/MD.0000000000026863

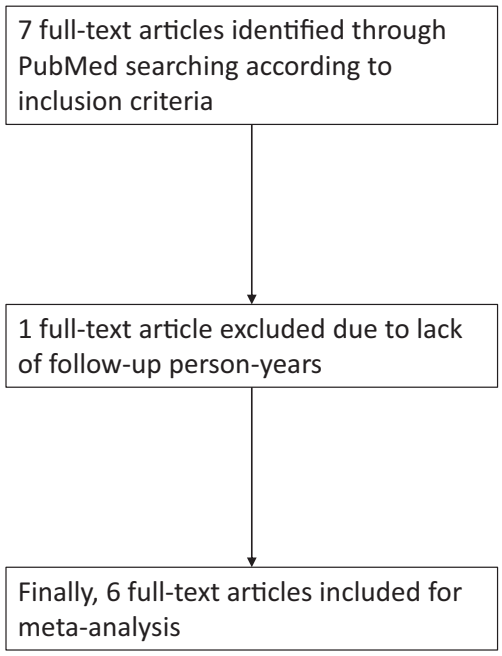

Figure 1. Flow diagram of literature search.

The association between inflammatory bowel disease and subsequent comorbidities has been investigated in previous meta-analysis, including depression, suicide, and others.[8–10] An immunocompromised status related to inflammatory bowel disease itself or caused by immunosuppressive/immunomodulatory therapy has placed these patients more susceptible to bacterial, viral, or fungal infections.[11–15] To date, existing epidemiological studies have shown that patients with inflammatory bowel disease are at higher risk of developing herpes zoster, but the incidence rates of herpes zoster in patients with inflammatory bowel disease varied from study to study, ranging from 7.54 per 1000 person-years to 18.34 per 1000 person-years.[16–22] Given the great variety of the incidence rate of herpes zoster, if more evidence can be found, decision-making on vaccination against herpes zoster will be definite. The aim of this meta-analysis was to investigate the incidence rate of herpes zoster among the population of inflammatory bowel disease.

2. Methods

2.1. Search strategy

PubMed was used to search literature published from January 2000 to July 2019.

The following key words were applied to find out literature of interest: "inflammatory bowel disease", "Crohn's disease", "ulcerative colitis", "herpes zoster", and "incidence". The inclusion criteria were as followings: cohort studies including subjects with a baseline diagnosis of inflammatory bowel disease, Crohn disease, and/or ulcerative colitis; cohort studies using herpes zoster as a primary outcome. Figure 1 presents the flow diagram of literature search.

2.2. Data extraction

The qualification of each searched article was assessed by 3 authors according to the aforementioned key words and inclusion criteria (KFL, CLL, and YHK). Data on the following variables were extracted: the last name of the first author, the year of publication, the country where the study was conducted, the case number of inflammatory bowel disease, the case number of non-inflammatory bowel disease, the event number of herpes zoster, the follow-up person-years, and the incidence rate of herpes zoster. Disagreements were resolved through discussion and consensus with the 2 authors (CSL and BFH).

2.3. Major outcome

The major outcome was a new diagnosis of herpes zoster in patients previously diagnosed with inflammatory bowel disease.

2.4. Statistical analysis

The pooled estimate of the incidence rate ratio (IRR) and 95% confidence interval (CI) was calculated to investigate the association between inflammatory bowel disease and herpes zoster. Statistical heterogeneity was assessed based on the I2 statistics, with $I2 > 50\%$ meaning significant heterogeneity. A random-effects model was applied to combine an effect size if $I2 > 50\%$. Statistical analyses were performed by using STATA statistical software version 14 (College Station, TX: StataCorp LP). Statistical significance was reached if a $P < .05$ was obtained.

2.5. Statement of ethics

The study was conducted in accordance with the Declaration of Helsinki. The ethical approval was waived because the study was a meta-analysis of retrospective data.

3. Results

3.1. Characteristics of eligible studies

Table 1 demonstrated the characteristics of the eligible studies. Totally, 6 eligible cohort studies were identified through our

Table 1

Characteristics of eligible studies.

			Inflammatory bowel disease			Non-inflammatory bowel disease		
Author	Country	Year	Event number of herpes zoster	Person-years	Incidence*	Event number of herpes zoster	Person-years	Incidence*
Long et al, 2013	USA	2013	2677	364,533	7.34	4340	992,273	4.37
Tsai et al, 2015	Taiwan	2015	381	46,267	8.23	1068	185,902	5.74
Khan et al, 2018	USA	2018	321	42,511	7.55	1076	334,018	3.22
Chang et al, 2018	Korea	2018	2340	127,621	18.34	2,828,257	250,552,299	11.29
Soh et al, 2019	Korea	2019	2071	142,729	14.51	6672	726,007	9.19

* Incidence: incidence rate, per 1000 person-years.

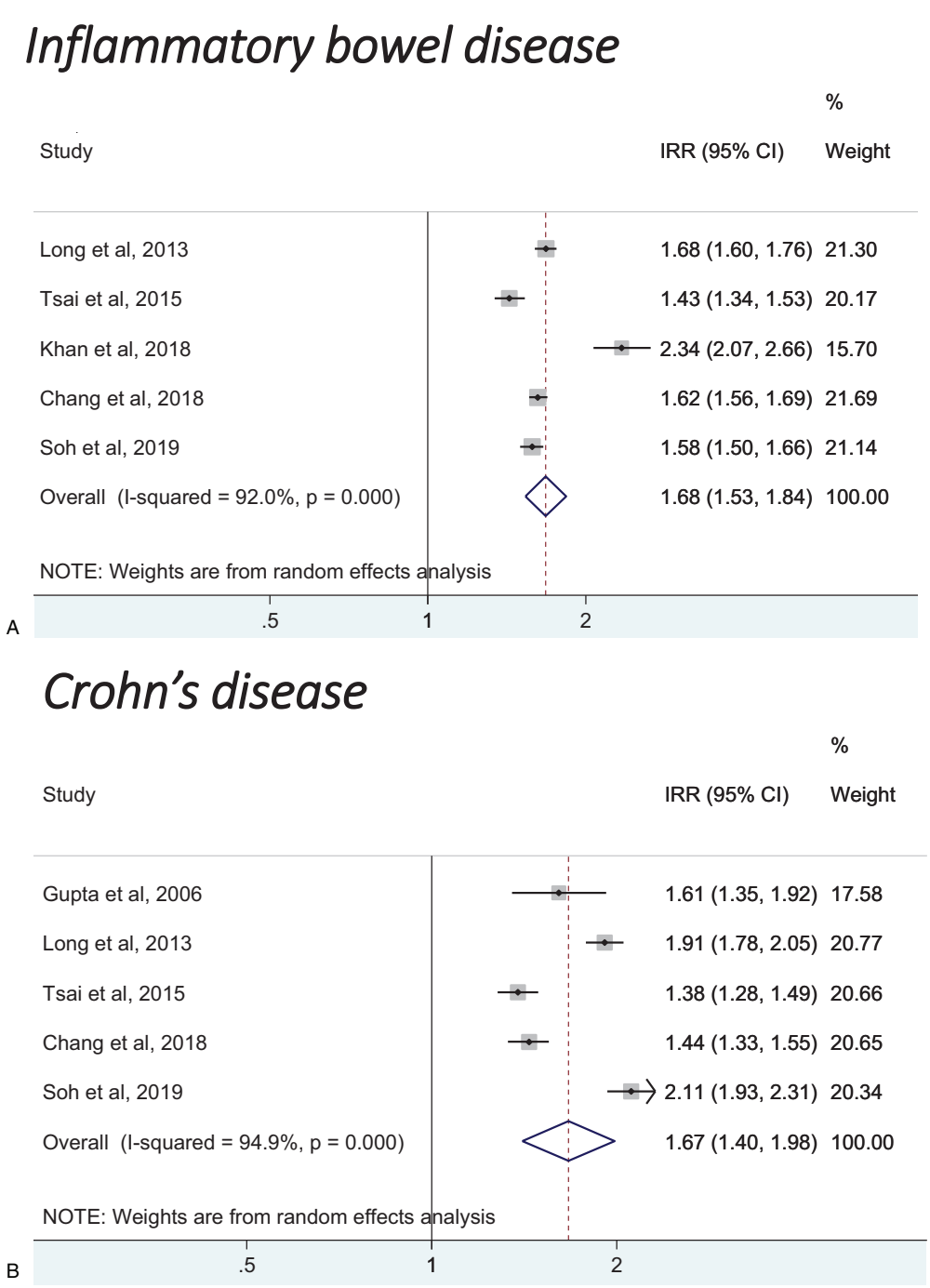

Figure 2. (A) Forest plot demonstrating the incidence rate ratio of herpes zoster between patients with inflammatory bowel disease and non-inflammatory bowel disease controls (IRR = 1.68, 95% CI = 1.53–1.84). (B) Forest plot demonstrating the incidence rate ratio of herpes zoster between patients with Crohn disease and non-inflammatory bowel disease controls (IRR = 1.67, 95% CI = 1.40–1.98). (C) Forest plot demonstrating the incidence rate ratio of herpes zoster between patients with ulcerative colitis and non-inflammatory bowel disease controls (IRR = 1.49, 95% CI = 1.34–1.65). 95% CI = 95% confidence interval, IRR = incidence rate ratio.

search strategy and were included in the meta-analysis. Gupta et al's study did not demonstrate the overall incidence rate of herpes zoster among patients with inflammatory bowel disease,[16] so it was not included in Table 1. There were 19753 patients with inflammatory bowel disease and 454 events of herpes zoster among 19753 patients with inflammatory bowel disease in Gupta et al's study.[16] The case number of inflammatory bowel disease ranged from 7055 to 108604. The event number of herpes zoster among patients with inflammatory bowel disease ranged from 321 to 2677. Totally, there were 216552 patients with inflammatory bowel disease and 7790 events of herpes zoster among 216552 patients with inflammatory bowel disease. However, Gupta et al's study demonstrated the individual IRR of herpes zoster among patients with Crohn disease or ulcerative colitis, so it was included in Figure 2(B) and (C). Khan et al's[19] study did not demonstrate the IRR of herpes

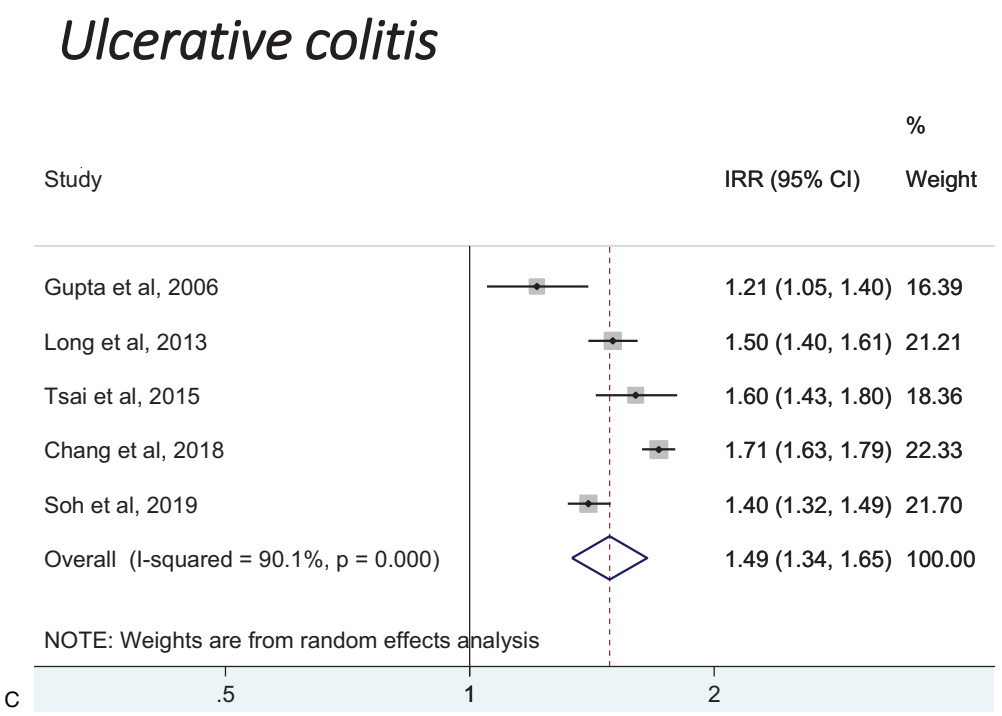

Figure 2. (Continued).

zoster among patients with Crohn disease or ulcerative colitis, but it demonstrated the overall incidence rate of herpes zoster in patients with inflammatory bowel disease. Therefore, Gupta et al's and Khan et al's studies were included for a partial meta-analysis.

3.2. Overall risk of herpes zoster

All eligible studies were pooled to investigate the impact of prior diagnosis of inflammatory bowel disease on the risk of developing herpes zoster. We estimated that the pooled incidence rate of herpes zoster in the inflammatory bowel disease group was 10.41 per 1000 person-years. The pooled incidence rate of herpes zoster in the non-inflammatory bowel disease group was 6.10 per 1000 person-years.

Figure 2(A) demonstrated that inflammatory bowel disease was associated with an increased risk of developing herpes zoster when compared with non-inflammatory bowel disease (IRR = 1.68, 95% CI = 1.53–1.84). The sub-analysis demonstrated that Crohn disease was associated with an increased risk of developing herpes zoster (IRR = 1.67, 95% CI = 1.40–1.98, Fig. 2(B)). Ulcerative colitis was associated with an increased risk of developing herpes zoster (IRR = 1.49, 95% CI = 1.34–1.65, Fig. 2(C)).

3.3. Assessment of study quality

The Newcastle-Ottawa Scale system was used to assess the quality of the included studies.[23] One of the 6 studies was scored as 7, and the scores of the other 5 studies were 8 (Table S1, Supplemental Digital Content, http://links.lww.com/MD2/A321). A Newcastle-Ottawa Scale score higher than 6 was considered as a high-quality study.

4. Discussion

In our meta-analysis, we observed that patients with inflammatory bowel disease were associated with a 1.68 times increased risk of developing herpes zoster. Similar risks were also detected in patients with Crohn disease and in patients with ulcerative colitis (IRR = 1.68 and IRR = 1.49, respectively). The underlying mechanism on the association between inflammatory bowel disease and herpes zoster was beyond the scope of our meta-analysis, we summarized the literature as follows. Inflammatory bowel disease itself can cause immune dysfunction and further places these patients at higher risk of developing bacterial, viral, or fungal infections.[11,15] In addition, drug-induced immunosuppression related to the treatments of inflammatory bowel disease also places these patients at higher risk of developing bacterial, viral, or fungal infections.[11–15]

All eligible studies included have shown the hazard ratio of developing herpes zoster. However, in the decision-making of public health and medical policy, it depends on the attributable risk rather than the hazard ratio. Without the data of incidence rate, the attributable risk cannot be estimated. In our meta-analysis, we estimated that the attributable risk of developing herpes zoster related to inflammatory bowel disease was 4.31 per 1000 person-years in our meta-analysis. As mentioned in previous articles,[24,25] inflammatory bowel disease cannot be preventable or curable, but herpes zoster can be preventable by vaccination. Live vaccines are generally contraindicated in patients with immunosuppressive status,[14,26] The CDC suggests that a live attenuated herpes zoster vaccine is contraindicated in patients on a substantially immunosuppressive steroid dose ≥2 weeks of daily receipt of 20 mg or 2 mg/kg body weight of prednisone or equivalent.[27] However, clinical studies demonstrated that patients with inflammatory bowel disease on

immunosuppressive or immuno-modulatory therapy did not have serious adverse events after receiving a live attenuated herpes zoster vaccine, and patients who received a live attenuated herpes zoster vaccine did not develop herpes zoster after vaccination during the study period.[28,29] According to the guidelines published by American College of Gastroenterology in 2017, all patient with inflammatory bowel disease aged 50 years and older should be suggested to receive 1 dose of live attenuated herpes zoster vaccine at least 1 month before starting immunosuppressive therapy.[30] Given that our meta-analysis supported patients with inflammatory bowel disease having a higher risk of developing herpes zoster, we suggest that the vaccination should be considered earlier than 50 years old and maybe at the time of inflammatory bowel disease being diagnosed.

To date, only 21% of patients with inflammatory bowel disease have received the herpes zoster vaccine because they were concerned of the efficacy and adverse events.[28,31] One cohort study demonstrated that the live attenuated herpes zoster vaccine could reduce the incidence of herpes zoster in patients with inflammatory bowel disease compared with those unvaccinated (4.09 vs 6.97 per 1000 patient-years).[32] In this cohort study, the number needed to vaccinate to prevent 1 case of herpes zoster is 347. In other word, only 1 case of inflammatory bowel disease would get the benefit from vaccination, but the other 346 cases did not get the benefit. Whether the cost-effectiveness of live attenuated herpes zoster vaccine is significant or not remains to be determined. A new adjuvanted recombinant herpes zoster vaccine has been proven to be cost-effective as compared with no vaccination, and to be cost-saving as compared with a live attenuated herpes zoster vaccine.[33–35] Observational studies have demonstrated that the number of patients who needed vaccination to prevent 1 event of herpes zoster was around 10 to 12 for the adjuvanted recombinant zoster vaccine and around 45 to 117 for the alive attenuated zoster vaccine.[36,37] In addition, the adjuvanted recombinant herpes zoster vaccine is not contraindicated in immunocompromised patients.[33,38] Further research is needed to determine the efficacy of the adjuvanted recombinant herpes zoster vaccine in patients with inflammatory bowel disease. The guidelines should be updated to suggest immunocompromised patients to receive recombinant instead of live vaccination.

5. Limitation

Some limitations need to be mentioned. First, theoretically we should compare patients with inflammatory bowel disease on pharmacotherapy and those patients not on pharmacotherapy. It was less likely to find patients with inflammatory bowel disease who did not take any medications. It was difficult to design a cohort study using such inclusion criteria. Some studies demonstrated that patients with inflammatory bowel disease who were exposed to thiopurines, anti-tumor necrosis factor-alpha, combination therapy, or corticosteroids were at increased risk for developing herpes zoster.[17,19] It was difficult to exclude the possibility that some treatment for inflammatory bowel disease would lead to an increased risk of developing herpes zoster in our meta-analysis. Second, not all relevant studies have shown the follow-up person-years. Without these data, it is difficult to measure the incidence rate of herpes zoster. We recommend that future studies investigating the incidence rate of herpes zoster should provide the event number and the follow-up person-years. Then researchers and scholars specializing in this field are able to test these published data. Third, age plays an important role on the risk of developing herpes zoster. Studies included did not provide the details of age distribution, so we were not able to measure the incidence rate of herpes zoster stratified by age. Similarly, our meta-analysis could not rule out the impacts of sex and other factors on the risk of developing herpes zoster. It indicates a future research direction that age, sex, and other factors should be included when conducting a meta-analysis of herpes zoster.

6. Conclusion

Patients with inflammatory bowel disease are at increased risk of developing herpes zoster. From a point of primary prevention, vaccination carries an indication to prevent future herpes zoster and postherpetic neuralgia. We suggest that the vaccination should be considered earlier than 50 years old and maybe at the time of inflammatory bowel disease being diagnosed. Great efforts should be made to elevate the vaccinated rate among these high risk patients.[31]

Author contributions

Shih-Wei Lai contributed to the conception of the article, initiated the draft of the article, and has approved the final draft submitted. Shih-Wei Lai and Kuan-Fu Liao contributed equally to the article. Kuan-Fu Liao, Cheng-Li Lin, and Yu-Hung Kuo conducted data analysis. Chiu-Shong Liu and Bing-Fang Hwang interpreted the data and contributed equally to the article.

Conceptualization: Shih-Wei Lai.

Formal analysis: Kuan-Fu Liao, Cheng-Li Lin, Yu-Hung Kuo, Chiu-Shong Liu, Bing-Fang Hwang.

Writing – original draft: Shih-Wei Lai.

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