Patients With Inflammatory Bowel Disease Are at Increased Risk for Complications of Herpes Zoster

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BACKGROUND & AIMS: **Patients with inflammatory bowel disease (IBD) are at an increased risk for vaccine-preventable diseases, such as herpes zoster (HZ). The aim of this study was to determine whether complications of HZ are more frequent in patients with IBD than in non-IBD controls.**

METHODS: **This was a retrospective, cohort study using the Optum Research Database. Patients with IBD were matched 1:1 to non-IBD controls based on age, sex, and index year, which was defined as the diagnosis of HZ. We then identified the complications of HZ that occurred up to 90 days after the index date. We compared patients with IBD with non-IBD controls and evaluated the 90-day risk of HZ complications. We used a composite primary outcome for any HZ complication. Secondary outcomes were risk factors for complications.**

RESULTS: **A total of 4756 patients with IBD met the inclusion criteria and were matched to the controls. Patients with IBD were more likely to have complications of HZ than controls (738 [15.52%] vs 595 [12.51%]; $P < .0001$). Patients with IBD with higher comorbidity scores were more likely to develop complications (1.86 vs 1.18; $P < .0001$). In the logistic regression analysis of patients with IBD having a higher comorbidity score, above 50 years of age, on anti-tumor necrosis factor (TNF) or corticosteroids were all at increased risk of a complication of HZ.**

CONCLUSION: **Patients with IBD are more likely to have complications of HZ than controls. Efforts are needed to increase HZ vaccine uptake to reduce the morbidity of HZ.**

Keywords: Herpes Zoster; Immunosuppression; Inflammatory Bowel Disease; Vaccines.

Inflammatory bowel disease (IBD) is a chronic inflammatory disorder of the gastrointestinal (GI) tract. Advances in the treatment of IBD include the use of monoclonal antibodies such as anti-tumor necrosis factor (TNF) alpha inhibitors and oral small molecules such as sphingosine 1 phosphate receptor (S1P) modulators and Janus kinase (JAK) inhibitors,[1] which can achieve higher rates of clinical remission than conventional therapy but are associated with an increased risk of infections, including herpes zoster (HZ).[2–4]

Patients with IBD are at a 2-fold increased risk of HZ, irrespective of whether they are on immunosuppressive therapy, compared with the general population.[5–7] Patients treated with thiopurines, anti-TNF, a JAK, or corticosteroids are at increased risk for HZ.[8,9] A recent systematic review with network meta-analysis

Abbreviations used in this paper: CD, Crohn's disease; CI, confidence interval; CPT, Current Procedural Terminology; GI, gastrointestinal; HZ, herpes zoster; HZV, herpes zoster vaccine; IBD, inflammatory bowel disease; ICD, International Classification of Diseases; IL, interleukin; JAK, Janus kinase; OR, odds ratio; PHN, post herpetic neuralgia; RZV, recombinant herpes zoster; S1P, sphingosine 1 phosphate receptor; SD, standard deviation; TNF, tumor necrosis factor; UC, ulcerative colitis; ZVL, live attenuated varicella zoster.

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evaluating the risk of HZ showed that JAKs, especially with increasing doses, had the highest risk.[10] Non-TNF biologics, anti-interleukin (IL)-23 antibodies, and anti-integrin antibodies, were not significantly associated with an increased risk of HZ. Those with repeated corticosteroid exposure or who have a flare of their IBD are also increased the risk of HZ.[9] Furthermore, in a recent hospital-based population-based study, HZ was one of the most frequent vaccine-preventable serious infections, accounting for one-third of all serious infections.[11] Although HZ is usually a self-limited disease in immunocompromised persons, zoster has the potential for disseminated and complicated disease.[12]

Immunosuppressed populations, including patients with IBD, are at risk of complications from HZ.[13,14] The most frequent complication of HZ is post herpetic neuralgia (PHN), which can lead to chronic neuropathic pain.[15] Other HZ complications include disseminated HZ, neurological, and/or ophthalmic complications.[16] Most of these complications (aside from PHN) are infrequent in the general population, but occur at higher rates in immunocompromised populations.[14] A recent systematic review that did not include patients with IBD found that HZ-associated complications are increased in immunocompromised populations.[14] There is a paucity of data regarding the frequency of these complications in patients with IBD.[17] The aim of this study was to determine if complications of HZ are more frequent in patients with IBD than in non-IBD controls. We hypothesized that patients with IBD who develop HZ would be at increased risk for complications of HZ compared with non-IBD controls with HZ due to their disease state and given that certain medication are independently associated with an increased risk of HZ.

What You Need to Know

Background

Individuals with inflammatory bowel disease (IBD) are at increased risk for vaccine-preventable diseases, notably herpes zoster (HZ), highlighting the importance of vaccination in this population.

Findings

Our retrospective study, analyzing 4756 patients with IBD matched with controls, revealed that those with IBD face a higher risk of HZ complications compared with non-IBD individuals.

Implications for patient care

Our study emphasizes the necessity of universally vaccinating all patients with IBD against HZ, irrespective of risk factors, to effectively mitigate complications and reduce overall morbidity.

Methods

Data Source

We performed a retrospective age-matched cohort study to determine whether patients with IBD are at an increased risk for complications of HZ compared with a non-IBD cohort. We also aimed to determine if certain immunosuppressive therapies were associated with an increased risk for complications of HZ. We conducted our study using de-identified medical and pharmacy administrative claims from a large database, OptumLabs Data Warehouse, which includes commercially insured and Medicare Advantage enrollees throughout the United States.[18]

We analyzed data from the periods of January 1, 2007, through April 1, 2022. OptumLabs has been used previously in multiple epidemiological studies evaluating the risk of serious infections[19,20] and the efficacy of medications in patients with IBD.[21,22] (Additional information of this database can be found in the Supplementary Methods). This study involved analysis of pre-existing de-identified data; it was exempted from institutional review board approval.[22]

Cohort Study

Patient selection. All patients with at least 12 months of baseline coverage, including pharmaceutical coverage, and 3 months after the diagnosis of HZ (index date), were eligible for the analysis. We identified patients with IBD based on the following 2 criteria: (1) at least 2 IBD-related inpatient or outpatient visits between 2007 and 2022; and (2) $\geq$1 outpatient pharmacy claims for any of the IBD treatment groups prior to diagnosis of HZ: (1) aminosalicylates; (2) thiopurine; (3) methotrexate; (4) anti-TNF agents (infliximab, adalimumab, certolizumab, golimumab); (5) vedolizumab; (6) tofacitinib; and (7) ustekinumab. Patients were considered to be on a drug if they had a pharmacy claim for oral medications within the previous 120 days or 180 days for any biologic medications. Using 2 International Classification of Diseases (ICD) codes along with an outpatient pharmacy claim have been conducted in multiple studies to identify IBD cohorts.[5,23] Each patient was classified as having either Crohn's disease (CD) or ulcerative colitis (UC). We used the CD and UC ICD-9 and ICD-10 codes (555. xx and K50.xx for CD, 556.xx and K51.xx for UC). We matched each patient with IBD to a non-IBD control (those who did not have a diagnosis of IBD or were on any medication used to treat IBD). We matched exactly on gender, region, race, year of birth, and length of follow-up. Patients matched on year of birth may enter the study period at different ages. Non-IBD controls were defined as those defined as those without a diagnosis of IBD (based on ICD-9 or ICD-10 codes) or being on any IBD-related medication other than corticosteroids. We also excluded those who we called IBD-similar, who had one ICD-9 or ICD-10 code for IBD.

Assessment of outcome. Our study cohort consisted of patients experiencing HZ as identified using the ICD-9, Clinical Modification (ICD-9 [0.53xx] or ICD-10 [B02.xx]) diagnosis code for zoster from either an inpatient or outpatient health care provider encounter.[5,24] Follow up started at the date which HZ was diagnosed (the 'index date'). All patients were required to have coverage at least 3 months after the index date; those who died within 90 days were excluded. We then identified the complications of HZ, based on previously used ICD-9 and ICD-10 codes in administrative claims database studies, that occurred up to 90 days after the index date (Supplementary Table 1).[24–28] These complications were defined as: (1) PHN; (2) multi-dermatomal involvement; (3) hospitalization; (4) ophthalmic involvement; (5) neurological complications; (6) zoster with other complications; and (7) multi-organ involvement (disseminated zoster). Using a composite primary outcome of any HZ complication over 90 days from HZ diagnosis, we compared patients with IBD and non-IBD age matched controls. Secondary outcomes evaluated included individual HZ complications, such as PHN. We also identified risk factors for complications of HZ among patients with IBD.

Covariates

Baseline covariates (12 months prior to index) included demographics: age, sex, race (gathered routinely by the database used), Census region, calendar year, comorbidity burden measured using the Charlson index (12-month baseline period and was calculated using prespecified algorithms[29]), prior medications, previous HZ vaccination (recombinant herpes zoster [RZV, Shingrix] and live attenuated varicella zoster virus vaccine (ZVL, Zostavax]), and antiviral drug use within 30 days on or after the index date. We pulled vaccinations based on the generic or brand name in medical or pharmacy claims for RZV vaccine (Shingrix) or ZVL virus vaccine (Zostavax) using Current Procedural Terminology (CPT) codes previously used to define HZ vaccine uptake (Supplementary Table 2).[30–32]

Statistical Analysis

Categorical variables were reported as frequencies (percentages) and continuous variables were reported as means (standard deviations [SDs]). A univariate logistic regression was performed to examine the association between each individual outcome and IBD group. The corresponding *P*-values, odds ratios (ORs), and 95% confidence intervals (CIs) were reported.

A subgroup analysis was performed among patients with IBD who had a composite complication vs those who did not have a complication. All the covariates used in the main analysis were used for the subgroup analysis, reported as frequencies (percentages) for categorical and mean (SD) for continuous variables. *P*-values were reported using the χ^2 test for categorical variables and the Student *t*-test for continuous variables. Among patients with IBD, a multivariable logistic regression was performed with composite complication as the outcome. All the above-mentioned covariates were used as predictors. We chose the variables in the model based off the standardized difference criteria. Any variables that were unbalanced, we controlled for in the model. The corresponding ORs, 95% CIs, and *P*-values were reported. All the analyses were performed using SAS Enterprise Guide 7.1 (SAS Institute Inc).

Results

A total of 1,660,773 patients with HZ were identified between January 1, 2007, and April 1, 2022. Of these, 627,411 had a diagnosis of HZ with enrollment 365 days prior and 90 days post HZV date of diagnosis. After applying the IBD criteria and cleaning any demographic anomalies in the data, we were left with 4760 patients with IBD and age $\pm$ 18 years (Figure 1). These patients with IBD were matched by age, sex, and by index year to non-IBD controls. The matching algorithm described produced 4756 patients in each of IBD cases and control groups. Patients with IBD had higher Charlson comorbidity scores compared with those without IBD (1.28 vs 0.93; *P* value $<$ .0001) (Table 1). No difference in prescription of anti-viral therapy after episode of HZ between the IBD and non-IBD controls group was seen (3671 [77.19%] vs 3638 [76.49%]; *P* value $=$ .4225). Most patients in both cohorts were not immunized (94.3% patients with IBD and 93.5% non-IBD controls) with either ZVL or the RZV series.

Complications of HZ

Patients with IBD were more likely to have a complication of HZ than non-IBD controls (738 [15.52%] vs 595 [12.51%]; *P* value $<$ .0001; OR, 1.28; 95% CI, 1.14–1.42; *P* value $<$ .0001). They were also more likely to have the following complications of HZ: hospitalization due to HZ, PHN, neurological complications, and disseminated zoster compared with non-IBD controls (Table 2). The most frequent complication of HZ was PHN in the IBD cohort (286 [6.01%]) and ophthalmic complications in the non-IBD cohort (238 [5.00%]). The absolute risk difference between the IBD and non-IBD group was 3.01%, and the number needed to harm was 33.

Predictors for Complications of HZ in the IBD Cohort

Patients with IBD who developed HZ complications were older (60.9 vs 53.4 years; *P* value $<$ .0001) and had higher comorbidity scores (1.86 vs. 1.18; *P* value $<$ .0001)

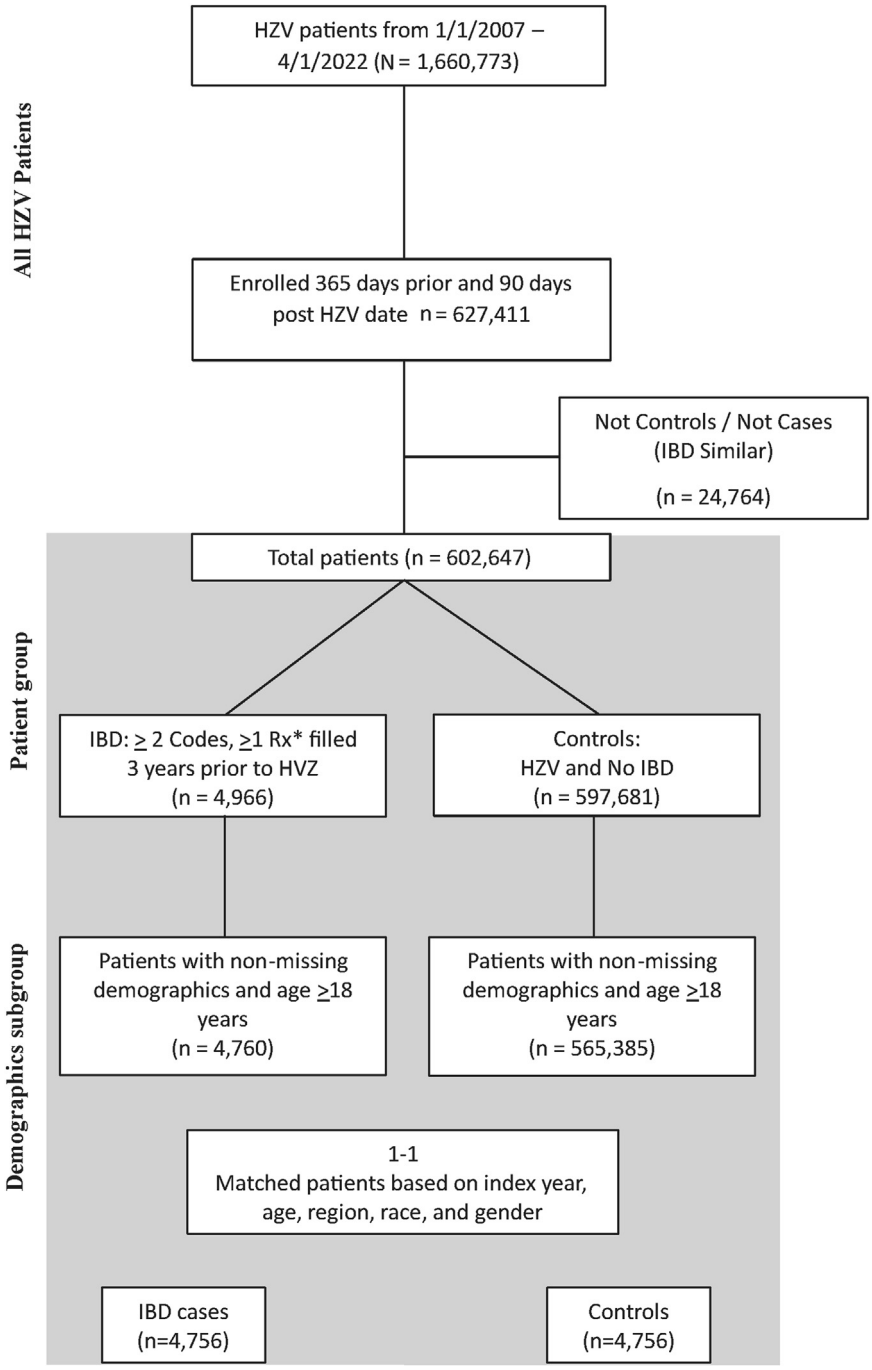


Figure 1. Flow diagram of patients with IBD and non-IBD controls. IBD cases were defined as prior IBD-related visits between 2007 and 2022 and outpatient pharmacy claims for IBD-related treatments. Cases were matched by age, sex, and by index year to non-IBD controls.

compared with those patients with IBD who did not develop a complication of HZ (Table 3). The use of antiviral therapy was more common in those with IBD who developed HZ complications (606 [82.11%] vs 3065 [76.28%]; *P* value = .0005). There was also no difference in HZ immunization rates (ZVL or RZV) among patients with IBD who developed a HZ complication and those who did not have a complication. Patients with IBD on prednisone were more likely to develop a complication of HZ (prednisone: 172 [23.31%] vs 744 [18.52%]; *P* value = .0024). No other IBD therapy was associated with a higher risk for a complication of HZ (Table 3).

Multivariable Analysis of any Complication of HZ in Patients With IBD

In logistic regression analysis, patients with IBD having congestive heart failure or having a history of cancer had an increased risk for complication of HZ. Patients with IBD above age 35 were at increased risk (OR, 1.56; 95% CI, 1.047–2.323; *P* value = .0287). Those above 50 years of age and older were at also increased risk (OR, 2.27; 95% CI, 1.55–3.32; *P* value < .0001), with those above age 65 having the highest risk (OR, 3.82; 95% CI, 2.55–5.74; *P* value < .0001) (Table 4). Prior

Table 1. Baseline Characteristics of the Cohort in IBD and Non-IBD Controls

Characteristic	IBD cases (N = 4756)	Non-IBD controls (N = 4756)	*P* value
Age, *years*	54.53 (±15.75)	54.52 (±15.75)	.9886
Age groups, *years*			.9996
18–34	574 (12.07)	571 (12.01)	
35–49	1201 (25.25)	1204 (25.32)	
50–64	1647 (34.63)	1648 (34.65)	
65+	1334 (28.05)	1333 (28.03)	
Female	2805 (58.98)	2805 (58.98)	
Race/ethnicity			1.0000
Asian	117 (2.46)	117 (2.46)	
Black	339 (7.13)	339 (7.13)	
White	3998 (84.06)	3998 (84.06)	
Hispanic	302 (6.35)	302 (6.35)	1.0000
Region			.9911
Midwest	1461 (30.72)	1460 (30.70)	–
Northeast	618 (12.99)	610 (12.83)	–
South	2049 (43.08)	2062 (43.36)	–
West	628 (13.20)	624 (13.12)	–
Type of IBD			–
CD	2305 (48.47)	0	–
UC	2264 (47.6)	0	–
IBD-unclassified	187 (3.93)	0	–
Charlson - sum of diseases	0.99 (± 1.44)	0.70 (± 1.17)	< .0001
Charlson - severity weighted sum of diseases	1.28 (± 2.08)	0.93 (± 1.70)	< .0001
Charlson index groups			< .0001
0–1	3411 (71.72)	3737 (78.57)	–
2–3	829 (17.43)	660 (13.88)	–
4+	516 (10.85)	359 (7.55)	–
Comorbidities[a]			
Myocardial infarction	121 (2.54)	81 (1.70)	.0044
Congestive heart failure	274 (5.76)	157 (3.30)	< .0001
Peripheral vascular disease	424 (8.92)	288 (6.06)	< .0001
Cerebrovascular disease	262 (5.51)	239 (5.03)	.2911
Dementia	77 (1.62)	62 (1.30)	.2000
Chronic obstructive pulmonary disease	831 (17.47)	616 (12.95)	< .0001
Peptic ulcer disease	103 (2.17)	30 (0.63)	< .0001
Mild liver disease	424 (8.92)	170 (3.57)	< .0001
Moderate/severe liver disease	36 (0.76)	<11 (<0.23)	.0001
Hemiplegia	21 (0.44)	17 (0.36)	.5156
Moderate/severe renal disease	321 (6.75)	260 (5.47)	.0090
Metastatic solid tumor	59 (1.24)	38 (0.80)	.0321
AIDS	12 (0.25)	11 (0.23)	.8346
Rheumatologic disease	379 (7.97)	106 (2.23)	< .0001
Other cancer	387 (8.14)	322 (6.77)	.0112
Hypertension	1965 (41.32)	1794 (37.72)	.0003
Diabetes	641 (13.48)	604 (12.70)	.2607
Depression	852 (17.91)	513 (10.79)	<.0001
Chronic kidney disease	204 (4.29)	159 (3.34)	.0160
Prior HZV			
ZVL	198 (4.16)	259 (5.45)	.0034
RZV	73 (1.53)	48 (1.01)	.0222
Antiviral 30 days after episode of HZV	3671 (77.19)	3638 (76.49)	.4225
Immunosuppresive therapy			
Anti-TNF therapy	1199 (25.21)	<11 (<0.23)	<.0001
Ustekinumab	26 (0.55)	<1 (<0.23)	<.0001
Vedolizumab	175 (3.68)	<11 (<0.23)	<.0001
Aminosalicylate therapy	2137 (44.93)	<11 (<0.23)	<.0001

Table 1. Continued

Characteristic	IBD cases (N = 4756)	Non-IBD controls (N = 4756)	*P* value
Thiopurine therapy	427 (8.98)	<11 (<0.23)	<.0001
Methotrexate	157 (3.30)	<11 (<0.23)	<.0001
Tofacitinib	19 (0.40)	<11 (<0.23)	<.0001
Prednisone	916 (19.26)	270 (5.68)	<.0001
Combination therapy[b]			
Anti-TNF therapy with thiopurine	337 (7.09)	<11 (<0.23)	<.0001
Anti-TNF therapy with methotrexate	85 (1.79)	<11 (<0.23)	<.0001
Ustekinumab with thiopurine	14 (0.29)	<11 (<0.23)	.0002
Ustekinumab with methotrexate	<11 (<0.23)	<11 (<0.23)	.0253

Note: Data are presented as number (%) or mean (standard deviation).
CD, Crohn's disease; HZV, herpes zoster virus; IBD, inflammatory bowel disease; RZV, recombinant herpes zoster; TNF, tumor necrosis factor; UC, ulcerative colitis; ZVL, live attenuated varicella zoster.
[a]Comorbidties defined per Charlson Index.
[b]Combination therapy: anti-TNF or ustekinumab with an immunomodulator (thiopurine or methotrexate).

receipt of the ZVL or RZV series was not associated with a lower risk of complications of HZ (Table 4). In regard to IBD medications, those on anti-TNF therapy (OR, 1.64; 95% CI, 1.31–2.05; *P* value < .0001) or prednisone (OR, 1.25; 95% CI, 1.02–1.54; *P* value = .0304) were associated with an increased risk for complications of HZ. No other IBD medications were associated with an increased risk for complications of HZ.

Discussion

In this nationwide study, patients with IBD showed a higher likelihood of HZ complications compared with non-IBD controls, with 15% experiencing complications. Patients with IBD had a 3% higher absolute risk of HZ complications, translating to a number needed to harm of 33. Risk factors for HZ complications in patients with IBD included older age, higher comorbidity scores, and treatment with anti-TNF therapy or prednisone. Non-TNF biologics and JAK inhibitors were not associated with increased risk. Antiviral treatment for HZ did not lower complication risk.

Patients with IBD were at increased risk for all complications of HZ except for ophthalmic complications, compared with non-IBD controls. PHN was the most frequent complication, occurring in 6% of the cohort and accounting for 36% of complications. This is consistent with a recent systemic review of immunosuppressed populations that did not include patients with IBD.[14] Although PHN may not result in hospitalization, it can lead to chronic neuropathic pain, depression, and disability.[33,34] Ophthalmic complications of HZ were seen in 5% of the cohort, which is higher than has been seen in other immunosuppressed populations <1%, but the IBD cohort was not at increased risk compared with non-IBD controls.[35–37] Disseminated HZ and hospitalization due to HZ occurred in 4% of the cohort and accounted for 23% of all complications, which is similar to the rates seen in the placebo group in 2 recent large randomized clinical vaccine trials in autologous hematopoietic cell transplantation.[14,38,39]

Table 2. Complications of HZ in Patients With IBD and Non-IBD Controls Within 90 Days of Index Case

Characteristic	IBD	Non-IBD Controls	Total	OR (95% CI)	*P* value
Hospitalization due to HZ	72 (1.51)	31 (0.65)	103	2.343 (1.535–3.5764)	< .0001
Zoster with post-herpectic involvement	286 (6.01)	208 (4.37)	494	1.399 (1.165–1.6804)	.0003
Zoster ophthalmic complications	251 (5.28)	238 (5.00)	489	1.058 (0.882–1.2689)	.5461
Zoster with neurological complications	196 (4.12)	131 (2.75)	327	1.517 (1.212–1.9001)	.0003
Zoster with other complications	128 (2.69)	100 (2.10)	228	1.288 (0.988–1.678)	.0605
Disseminated zoster	19 (0.40)	<11 (<0.23)		3.811 (1.422–10.215)	.0042
Had any complication (primary HZV)[a]	738 (15.52)	595 (12.51)	1,333	1.284 (1.143–1.443)	< .0001

Note: Data are presented as number (%) unless otherwise indicated.
CI, Confidence interval; HZ, herpes zoster; HZV, herpes zoster vaccine; IBD, inflammatory bowel disease; OR, odds ratio.
[a]Composite outcome of any of the above complications. Patients could have more than one complications (eg, zoster with ophthalmic complication that resulted in hospitalization).

Table 3. Predictors for Complications of HZV Among Patients With IBD

Characteristic	No complication (n = 4018)	Complications[a] (n = 738)	*P* value
Age, *years*	53.35 ± 15.66	60.94 ± 14.65	< .0001
Age groups, *years*			< .0001
18–34	534 (13.29)	40 (5.42)	–
35–49	1077 (26.80)	124 (16.80)	–
50–64	1388 (34.54)	259 (35.09)	–
65+	1019 (25.36)	315 (42.68)	–
Female	2360 (58.74)	445 (60.30)	0.4277
Race/ethnicity			0.7393
Asian	96 (2.39)	21 (2.85)	–
Black	284 (7.07)	55 (7.45)	–
White	3387 (84.30)	611 (82.79)	–
Hispanic	251 (6.25)	51 (6.91)	.4968
Region			.0385
Midwest	1231 (30.64)	230 (31.17)	–
Northeast	523 (13.02)	95 (12.87)	–
South	1710 (42.56)	339 (45.93)	–
West	554 (13.79)	74 (10.03)	–
Charlson - sum of diseases	0.91 (1.38)	1.39 (1.65)	< .0001
Charlson - severity weighted sum of diseases	1.18 ± 1.97	1.86 ± 2.52	< .0001
Charlson index groups			< .0001
0–1	2963 (73.74)	448 (60.70)	
2–3	666 (16.58)	163 (22.09)	
4+	389 (9.68)	127 (17.21)	
Comorbidties[b]			
Myocardial infarction	92 (2.29)	29 (3.93)	.0093
Congestive heart failure	204 (5.08)	70 (9.49)	< .0001
Peripheral vascular disease	324 (8.06)	100 (13.55)	< .0001
Cerebrovascular disease	208 (5.18)	54 (7.32)	.0192
Dementia	59 (1.47)	18 (2.44)	.0548
Chronic obstructive pulmonary disease	659 (16.40)	172 (23.31)	< .0001
Peptic ulcer disease	82 (2.04)	21 (2.85)	.1675
Mild liver disease	345 (8.59)	79 (10.70)	.0634
Moderate/severe liver disease	26 (0.65)	<11 (<1.49)	.0414
Hemiplegia	18 (0.45)	<11 (<1.49)	.8759
Moderate/severe renal disease	255 (6.35)	66 (8.94)	.0098
Metastatic solid tumor	42 (1.05)	17 (2.30)	.0045
AIDS	<11 (<0.27)	<11 (<1.49)	.9123
Rheumatologic disease	299 (7.44)	80 (10.84)	.0017
Other cancer	288 (7.17)	99 (13.41)	< .0001
Hypertension	1572 (39.12)	393 (53.25)	< .0001
Diabetes	504 (12.54)	137 (18.56)	< .0001
Depression	704 (17.52)	148 (20.05)	.0991
Chronic kidney disease	153 (3.81)	51 (6.91)	.0001
Prior HZV			
ZVL	162 (4.03)	36 (4.88)	.2901
RZV	62 (1.54)	11 (1.49)	.9150
Antiviral within 30 days after episode of HZV	3065 (76.28)	606 (82.11)	.0005
Immunosuppresive therapy			
Anti-TNF therapy	1002 (24.94)	197 (26.69)	.3126
Ustekinumab	22 (0.55)	<11 (<1.49)	.9851
Vedolizumab	150 (3.73)	25 (3.39)	.6466
Aminosalicylate therapy	1823 (45.37)	314 (42.55)	.1564
Thiopurine	373 (9.28)	54 (7.32)	.0859
Methotrexate	128 (3.19)	29 (3.93)	.2985
Tofacitinib	17 (0.42)	<11 (<1.49)	.5471
Prednisone	744 (18.52)	172 (23.31)	.0024
Anti-TNF, ustekinumab, thiopurine, or methotrexate	1371 (34.12)	262 (35.50)	.4681

Table 3. Continued

Characteristic	No complication (n = 4018)	Complications[a] (n = 738)	*P* value
Combination therapy[c]			
Anti-TNF therapy with thiopurine	292 (7.27)	45 (6.10)	.2550
Anti-TNF therapy with methotrexate	69 (1.72)	16 (2.17)	.3956
Ustekinumab with thiopurine	13 (0.32)	<11 (<1.49)	.3861
Ustekinumab with methotrexate	<11 (<0.27)	<11 (<1.49)	.7818

Note: Data are presented as number (%) or mean (standard deviation).
CD, Crohn's disease; HZV, herpes zoster virus; IBD, inflammatory bowel disease; RZV, recombinant herpes zoster; TNF, tumor necrosis factor; UC, ulcerative colitis; ZVL, live attenuated varicella zoster.
[a]Complications included post-herpetic neuralgia (PHN); multi-dermatomal involvement; hospitalization; ophthalmic involvement; neurological complications; multi-organ involvement (disseminated zoster). These complications were assessed within 90 days of the index case.
[b]Comorbidities defined per Charlson Index.
[c]Combination therapy: Anti-TNF or ustekinumab with an immunomodulator (thiopurine or methotrexate).

When evaluating risk factors for complications of HZ among the IBD cohort, patients 50 years of age and older were at increased risk, with those above age 65 having the highest risk. Patients with higher comorbidity scores were more likely to have a complication of HZ. Use of corticosteroids or anti-TNF therapy were associated with an increased risk for complications. Tofacitinib or thiopurines, 2 IBD medications well-known to be associated with an increased risk of HZ, were not associated with an increased risk for complications,[7,8] but this may be due to small sample size of both of these drugs. The majority of patients with IBD (>95%) lacked HZ immunization with RZV, despite 63% being over 50 years of age and above. Low immunization rates (4% ZVL, 1.5% RZV) limited assessment of vaccine effectiveness against HZ complications.

Table 4. Multivariable Analysis of Predictors for Complications[a] Related to HZV Among Patients with IBD

Variables	OR (95% CI)	*P* value
Age groups, years (Ref 18–34)		
35–49	1.56 (1.047–2.323)	.0287
50–64	2.27 (1.547–3.329)	< .0001
65+	3.827 (2.551–5.74)	< .0001
Gender (Ref. female)		
Male	1.01 (0.839–1.216)	.9171
Race (Ref. White)		
Asian	1.277 (0.739–2.207)	.3815
Black	0.934 (0.659–1.323)	.7006
Hispanic	1.092 (0.769–1.551)	.6217
Charlson index score (Ref. 0–1)[b]		
>1–2	1.319 (1.005–1.731)	.0462
>2–4	1.476 (1.12–1.944)	.0057
>4	1.788 (1.332–2.4)	.0001
Prior HZV		
ZVL	0.881 (0.579–1.342)	.5564
RZV	0.583 (0.27–1.26)	.1703
Antiviral within 30 days after HZV	1.329 (1.06–1.667)	.0139
Immunosuppressive therapy		
Anti-TNF therapy	1.64 (1.309–2.054)	< .0001
Ustekinumab	1.553 (0.405–5.948)	.5208
Vedolizumab	1.136 (0.677–1.907)	.6284
Aminosalicylic acid (ASA)	0.967 (0.796–1.173)	.7323
Thiopurine	0.84 (0.582–1.213)	.3526
Methotrexate	0.87 (0.522–1.448)	.5916
Tofacitinib	1.096 (0.239–5.017)	.9059
Prednisone	1.253 (1.022–1.537)	.0304

CI, Confidence interval; IBD, inflammatory bowel disease; HZV, herpes zoster vaccine; OR, odds ratio; RZV, recombinant herpes zoster; TNF, tumor necrosis factor; ZVL, live attenuated varicella zoster.
[a]Complications included post-herpetic neuralgia (PHN); multi-dermatomal involvement; hospitalization; ophthalmic involvement; neurological complications; multi-organ involvement (disseminated zoster). These complications were assessed within 90 days of the index case.
[b]Comorbidities defined per Charlson Index.

A previous study using the Nationwide Veterans affairs database did not find that patients with IBD treated with anti-TNF therapy had an increased risk of complications of HZ compared with those on aminosalicylates.[24] In that study, 23% of patients (69 of 295) developed a complication of HZ, with PHN being the most common (55%) followed by ophthalmic complications of HZ (21%). Our study was able to evaluate a larger sample size with greater than 4000 patients with IBD, on a greater range of immune-modifying therapy. Our findings are generalizable to all patients with IBD, not just those dosed on TNF biologic therapy, given that 54% of our cohort was on aminosalicylate therapy or a thiopurine. This would suggest that all patients with IBD, regardless of treatment regimen, are at risk for complications of HZ.

Few studies explore the biology behind HZ risks in high-risk populations. Lower TNF-α levels correlate with more severe HZ, particularly in patients developing PHN.[40] Prednisone's anti-inflammatory effects, including cytokine inhibition, may reduce VZV replication inhibition. Blood from corticosteroid-treated patients showed decreased viral spread inhibition.[41] Consequently, anti-TNF therapy or prednisone may contribute to HZ complications by suppressing the body's natural antiviral mechanisms.

Our study has several strengths, including its large sample size; broad spectrum of treatment for IBD regimens; its design, which evaluated whether patients with

IBD were at increased risk for complications of HZ; and validated claim codes for HZ and complications of HZ. The retrospective analysis of claim databases has several inherent limitations such as relying on ICD-9/10-CM diagnosis codes to identify disease conditions and pharmacy claims, which do not guarantee filling of medication. Our study has several limitations beyond those inherent to retrospective designs. The small sample size for non-TNF biologics and JAK inhibitors limited our ability to assess their association with HZ complications. Further studies needed on JAK inhibitors' impact. Low RZV immunization rates prevented us from determining its protective effect against HZ complications. We lacked data on disease activity measures, though prednisone use (a potential proxy for disease flares) was associated with increased HZ complications, consistent with previous findings.[9] The higher comorbidity scores in the IBD cohort compared with non-IBD controls may have contributed to their increased risk of HZ complications.

Conclusion

In conclusion, this study serves as a call to action for gastroenterologists in addressing the elevated risk of HZ complications in patients with IBD. By leveraging the risk factors and medication associations identified in our study, and the proven benefits of vaccination in other studies, gastroenterologists can optimize patient care and contribute to reducing the burden of HZ-related complications.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2024.09.022.

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Conflicts of interest
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Data Availability
The data underlying this article were provided with permission by OptumLabs. Data will be shared on request to the corresponding author with permission of OptumLabs.

Supplementary Methods

The database contains data of more than 100 million enrollees from geographically diverse regions across the United States. Medical claims include the Internal Classification of Diseases, Ninth Revision and Tenth Revision, Clinical Modification (ICD-9-CM; ICD-10- CM) diagnosis codes, ICD-9 and ICD-10 procedure codes, Current Procedural Terminology, Fourth Edition (CPT-4) procedure codes, Healthcare Common Procedure Coding System (HCPCS) procedure codes, site of service codes, and provider specialty codes. All study data were accessed using techniques compliant with the Health Insurance Portability and Accountability Act of 1996

For patients who had ICD-9 or ICD-10 claims codes for both Crohn's disease (CD) and ulcerative colitis (UC), disease assignment was made according to the majority of the last seven claims or the majority of total claims if there were fewer than 7. If there were equal numbers of claims for CD and UC, the individuals were classified as IBD-unspecified.

Supplementary Table 1. ICD-9/10 Codes for HZ and Complications of HZ

HZ disease	ICD-9 diagnosis code	
HZ	053	Uncomplicated
HZ with meningitis	053.0	Neurologic complication
HZ with other nervous system complications	053.1	Neurologic complication
HZ with unspecified nervous system complication	053.10	Neurologic complication
Geniculate HZ	053.11	Neurologic complication
HZ myelitis	053.14	Neurologic complication
HZ with other nervous system complications	053.19	Neurologic complication
HZ with ophthalmic complications	053.2	Ophthalmic complication
HZ dermatitis of eyelid convert	053.20	Ophthalmic complication
HZ keratoconjunctivitis convert	053.21	Ophthalmic complication
HZ iridocyclitis convert	053.22	Ophthalmic complication
HZ with other ophthalmic complications convert	053.29	Ophthalmic complication
HZ with other specified complications	053.7	Other complication of HZ
Otitis externa due to HZ	053.71	Other complication of HZ
HZ with other specified complications	053.79	Other complication of HZ
HZ with unspecified complication	053.8	Disseminated zoster
Post-herpetic trigeminal neuralgia	053.12	PHN
Post-herpetic polyneuropathy	053.13	PHN
	ICD-10 diagnosis code	
Zoster meningitis	B02.1	Neurologic complication
Postherpetic geniculate ganglionitis	B02.21	Neurologic complication
Postherpetic myelitis	B02.24	Neurologic complication
Other postherpetic nervous system involvement	B02.29	Neurologic complication
Zoster keratitis	B02.33	Ophthalmic complication
Zoster iridocyclitis	B02.32	Ophthalmic complication
Other HZ eye disease	B02.39	Ophthalmic complication
Zoster with other complications	B02.8	Other complication of HZ
Postherpetic trigeminal neuralgia	B02.22	PHN
Post-herpetic polyneuropathy	B02.23	PHN
Disseminated zoster	B02.7	

HZ, Herpes zoster; ICD, International Classification of Diseases; PHN, post herpetic neuralgia.

Supplementary Table 2. Codes for HZVs

HZV	CPT code
RZV (Shingrix)	≥1 CPT codes in any position: 90750 in medical and pharmacy claims
ZVL (Zostavax)	1 CPT codes in any position: 90736

CPT, Current Procedural Terminology; HZV, herpes zoster vaccine; RZV, recombinant herpes zoster; ZVL, live attenuated varicella zoster.