Open Forum Infectious Diseases

MAJOR ARTICLE

Increased Risk of Herpes Zoster in Adults ≥50 Years Old Diagnosed With COVID-19 in the United States

Amit Bhavsar,[1] Germain Lonnet,[2] Chengbin Wang,[3] Konstantina Chatzikonstantinidou,[4] Raunak Parikh,[1] Yves Brabant,[1] Nathalie Servotte,[1] Meng Shi,[3] Robyn Widenmaier,[3] and Emmanuel Aris[1]

[1]GSK, Wavre, Belgium, [2]Business & Decision Life Sciences, Brussels, Belgium, c/o GSK, Wavre, Belgium, [3]GSK, Rockville, Maryland, USA, and [4]Aixial, an Alten Company, Brussels, Belgium, c/o GSK, Wavre, Belgium

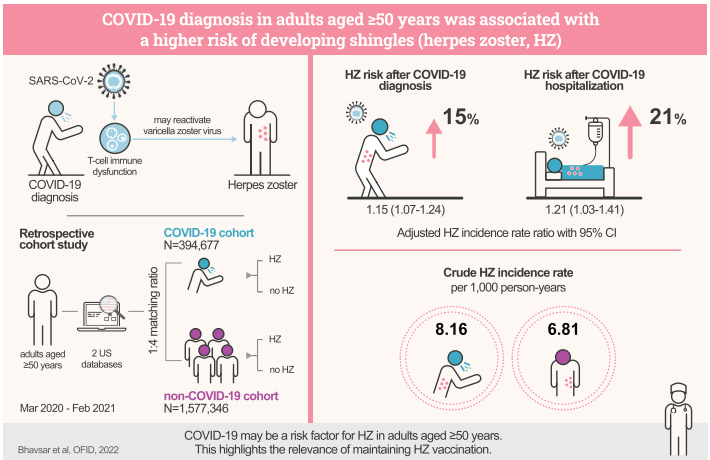
Background. Case reports have described herpes zoster (HZ) in patients with coronavirus disease 2019 (COVID-19). However, this constitutes low-quality evidence for an association. We therefore performed a retrospective cohort study to assess the risk of developing HZ following a COVID-19 diagnosis.

Methods. We compared the HZ incidence in ≥50-year-olds diagnosed with COVID-19 vs those never diagnosed with COVID-19. We used data from the US MarketScan Commercial Claims and Encounters and Medicare Supplemental (3/2020–2/2021) and Optum Clinformatics Data Mart (3–12/2020) databases. Individuals with COVID-19 were exact-matched 1:4 to those without COVID-19 by age, sex, presence of HZ risk factors, and health care cost level. Adjusted incidence rate ratios (aIRRs) were estimated by Poisson regression.

Results. A total of 394 677 individuals ≥50 years old with COVID-19 were matched with 1 577 346 individuals without COVID-19. Mean follow-up time after COVID-19 diagnosis and baseline characteristics were balanced between cohorts. Individuals diagnosed with COVID-19 had a 15% higher HZ risk than those without COVID-19 (aIRR, 1.15; 95% CI, 1.07–1.24; $P < .001$). The increased HZ risk was more pronounced (21%) following COVID-19 hospitalization (aIRR, 1.21; 95% CI, 1.03–1.41; $P = .02$).

Conclusions. We found that COVID-19 diagnosis in ≥50-year-olds was associated with a significantly increased risk of developing HZ, highlighting the relevance of maintaining HZ vaccination.

Graphical Abstract



Keywords. coronavirus; COVID-19; herpes zoster; SARS-CoV-2; shingles.

Herpes zoster (HZ), also known as shingles, is caused by reactivation of latent varicella zoster virus (VZV) and is characterized by a painful, vesicular, dermatomal rash [1, 2]. Risk factors for HZ include older age—with a sharp increase in incidence seen after 50 years of age—and immunosuppression (eg, in transplant recipients, persons with malignancies, or those on immunosuppressive medications) [2–5]. The elevated HZ risk in these populations is thought to be a consequence of a decline in VZV-specific cell-mediated immunity below a threshold required to maintain latency of the virus [2, 4].

Received 18 January 2022; editorial decision 26 February 2022; accepted 7 March 2022; published online 9 March 2022.

Correspondence: Amit Bhavsar, MBBS, MHA, GSK, Avenue Fleming 20, 1300 Wavre, Belgium (amit.b.bhavsar@gsk.com).

Open Forum Infectious Diseases®2022

https://doi.org/10.1093/ofid/ofac118

Since the start of the coronavirus disease 2019 (COVID-19) pandemic [6], several case reports and case series have been published describing HZ cases in COVID-19 patients, often occurring within 1 week of COVID-19 diagnosis or COVID-19 hospitalization [7]. A descriptive analysis of data from Brazil's Ministry of Health showed a 35% increase in HZ diagnoses between March and August 2020 compared with the same periods in 2017–2019 [8]. Similarly, a doubling in HZ infections was seen in an outpatient clinic in Turkey in May and June 2020 compared with the same period in 2019 [9]. It was previously hypothesized that infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) could lead to VZV reactivation as a result of SARS-CoV-2-induced T-cell immune dysfunction [7, 10–14]. While it is biologically plausible that SARS-CoV-2 infection triggers HZ, there is currently no strong epidemiological evidence available that assesses HZ risk in COVID-19 patients. We therefore performed a retrospective cohort study based on administrative health claims data to assess if individuals who had been diagnosed with COVID-19 were more likely to develop HZ than those never diagnosed with COVID-19. We focused on ≥50-year-olds because they are at increased risk of both HZ and severe COVID-19 [2, 3, 15, 16].

METHODS

Study Design and Data Source

We performed a retrospective cohort study using data from the Truven MarketScan Commercial Claims and Encounters (CCAE) and Medicare Supplemental (MS) databases (from March 13, 2020, to February 28, 2021) and the Optum Clinformatics Data Mart database (from March 13 to December 31, 2020). The MarketScan CCAE and MS databases contain inpatient and outpatient claims as well as outpatient prescription drug claims for >39.7 million people (annually) from >120 large employers and >40 health plans in the United States [17]. We supplemented these data with the MarketScan CCAE and MS early view data sets, in which data are available within 45 days of the end of the service month. The Optum Clinformatics Data Mart database contains information on medical claims, prescription drugs, and outpatient laboratory tests from >87 million individuals (total) in the United States insured with a commercial health plan or Medicare Advantage plan. No overlap is expected between the MarketScan and Optum databases.

Both databases are pseudonymized and compliant with the Health Insurance Portability and Accountability Act. The study did therefore not need ethics committee approval.

Outcomes

As our primary outcome, we compared the HZ incidence in ≥50-year-olds who had been diagnosed with COVID-19 with that in ≥50-year-olds never diagnosed with COVID-19. We also assessed the HZ incidence in ≥50-year-olds following different time intervals since COVID-19 diagnosis and following COVID-19 hospitalization. Finally, we evaluated the HZ incidence in different age groups of adults ≥18 years old with vs without COVID-19 diagnosis (Supplementary Data).

Study Population and Definitions

For the primary analysis, 2 cohorts were defined: a COVID-19_50+ cohort, with individuals who had a first-time COVID-19 event during the study, and an exact-matched non-COVID-19_50+ cohort, with individuals who had no COVID-19 event and no clinically–epidemiologically diagnosed, probable, or suspected COVID-19 event at any time during or before the study. A COVID-19 event was defined by the occurrence of an inpatient or outpatient claim with a COVID-19 diagnosis based on International Classification of Diseases, 10th revision (ICD-10), codes in which SARS-CoV-2 was identified; the ICD-10 code for clinically–epidemiologically diagnosed, probable, or suspected COVID-19 was not considered to identify COVID-19 cases for inclusion in the COVID-19_50+ cohort (Supplementary Data). The index date for individuals in the COVID-19_50+ cohort was the date of the first COVID-19 event during the study. The index date for individuals in the non-COVID-19_50+ cohort was the index date of the corresponding matched individual in the COVID-19_50+ cohort.

Both cohorts included individuals ≥50 years old on March 13, 2020, registered in the above-mentioned MarketScan or Optum databases, with at least 365 days of continuous follow-up until the index date (allowing gaps of maximum 7 days). To be eligible, individuals could have no history of HZ (based on ICD-9 and ICD-10 codes) (Supplementary Data) and no history of vaccination against COVID-19 or HZ (based on National Drug Codes and Current Procedural Terminology codes) (Supplementary Data) before or on the index date.

Matching was performed separately in the MarketScan and Optum databases, based on age stratum (50–59, 60–64, 65–74, 75–84, and ≥85 years), sex, presence of at least 1 immunocompromising condition or other risk factor for HZ (Table 1) (Supplementary Data), and health care cost level within 183 days before March 13, 2020 (<30th percentile of the cost distribution of the COVID-19_50+ cohort, 30th–<70th percentile, and ≥70th percentile). We matched each COVID-19_50+ individual with up to 4 non-COVID-19_50+ individuals, selected randomly within each combination of matching variables. We had originally planned to only select individuals with a health care claim within 15 days of the index date of the corresponding COVID-19_50+ person. However, this requirement was dropped because it created selection bias by favoring individuals with many visits (ie, possibly unhealthier) as controls.

To evaluate the HZ risk in ≥50-year-olds who had been hospitalized with COVID-19, a subset of the COVID-19_50+ cohort

Table 1. Immunocompromising Conditions and Risk Factors Included in the Matching Algorithm

Immunocompromising Conditions
HIV or AIDS (excluding asymptomatic HIV)
Hematologic malignancy
Other intrinsic immune conditions
Solid malignancy[a]
Organ transplant[a]
Rheumatologic or inflammatory conditions[b]
Individuals who received chemotherapy, immunosuppressive medications (any duration), or systemic corticosteroids for ≥14 d
Risk Factors
Rheumatoid arthritis
Inflammatory bowel disease
Chronic obstructive pulmonary disease
Asthma
Chronic kidney disease
Diabetes with or without complication
Depression

See the Supplementary Data for information on how these were identified.

[a]If receiving chemotherapeutic or immune-modulating agents.

[b]If receiving chemotherapeutic or immune-modulating agents or systemic corticosteroids.

was used that included individuals with a COVID-19-associated inpatient claim within 21 days of the first COVID-19 diagnosis (as it was previously shown that for most COVID-19 patients, the time between first symptom and hospitalization was <21 days [18, 19]). Their matches from the non-COVID-19_50+ cohort were used as controls.

Individuals were followed for the occurrence of HZ from the day after the index date until the end of continuous enrollment (ie, insurance coverage interrupted for ≥7 consecutive days), HZ diagnosis, HZ or COVID-19 vaccination, death, or study end, whichever came first. An HZ event was defined by the occurrence of either an inpatient claim with an HZ diagnosis (identified by ICD-10 codes) (Supplementary Data) *or* 2 outpatient claims with HZ diagnoses no more than 30 days apart *or* 1 outpatient claim with an HZ diagnosis and a pharmacy claim for antiviral treatment (Supplementary Data) within 7 days before or after the HZ diagnosis claim.

Sensitivity Analyses

To assess the robustness of the study design, we performed a sensitivity analysis using fractures as control exposure because we expected there would be no association between fractures and HZ. Fractures were defined by a claim with an arm, leg, hand, or foot fracture diagnosis, identified by ICD-10 codes (Supplementary Data). We avoided fractures most commonly associated with osteoporosis (eg, hip and vertebral fractures) to limit possible confounding. A fracture cohort and an exact-matched nonfracture cohort of ≥50-year-olds were defined using similar criteria as the non-COVID-19_50+ cohort and using the same matching variables. Individuals in the fracture cohort had a fracture event during the study period but not during the 183 days before March 13, 2020, while individuals in the nonfracture cohort had no fracture events during the study or the preceding 183 days. The index date was defined as for the COVID-19 analysis but using the date of the first fracture diagnosis during the study.

To assess the impact of the COVID-19 case definition, we performed a sensitivity analysis with a more specific definition of a COVID-19 event, identified either as 1 inpatient claim with a COVID-19 diagnosis or at least 2 outpatient claims with a COVID-19 diagnosis no more than 30 days apart.

Statistical Methods

A feasibility assessment indicated that the available data would provide enough power to detect an increased risk in the COVID-19_50+ cohort vs the non-COVID-19_50+ cohort (Supplementary Data).

We descriptively analyzed baseline characteristics (such as age, sex, health care cost, immunocompromising conditions, and other risk factors for HZ) for the different cohorts using frequencies and proportions for categorical variables and mean and SD for continuous variables. The standardized mean difference (SMD) was calculated to evaluate whether baseline characteristics were balanced between matched cohorts; variables with an SMD >0.2 were considered for inclusion as covariates in the Poisson regression model.

Crude HZ incidence rates in ≥50-year-olds with vs without COVID-19 (and in those with COVID-19 hospitalization vs without COVID-19) were calculated by dividing the number of observed HZ cases by the total number of person-years in each cohort. The adjusted incidence rate ratio (aIRR) was estimated based on HZ incidence rates modeled by Poisson regression, with age stratum (≥65 years vs 50–64 years), sex, database (MarketScan or Optum), and other possible confounders as covariates and time in years as offset. Only variables with a statistically significant effect were kept in the model (by backward selection), except the effect of COVID-19, which was always kept.

Similar models were considered to calculate the aIRRs for different time intervals after the index date (1–30, 31–90, 91–183, and >183 days) in ≥50-year-olds for the different age groups and for the sensitivity analyses.

Missing data were not imputed. Statistical analyses were performed using SAS software, version 9.04.01 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Participants

A total of 1 449 224 individuals in the MarketScan and Optum databases had a COVID-19 diagnosis during the study, of whom 642 696 were ≥50 years old. Of these, 394 677 met inclusion criteria and were part of the COVID-19_50+ cohort. The non-COVID-19_50+ cohort included 1 577 346 matched individuals (Figure 1). The mean length of follow-up after the index date (SD) was similar in both cohorts: 98.85 (80.99)

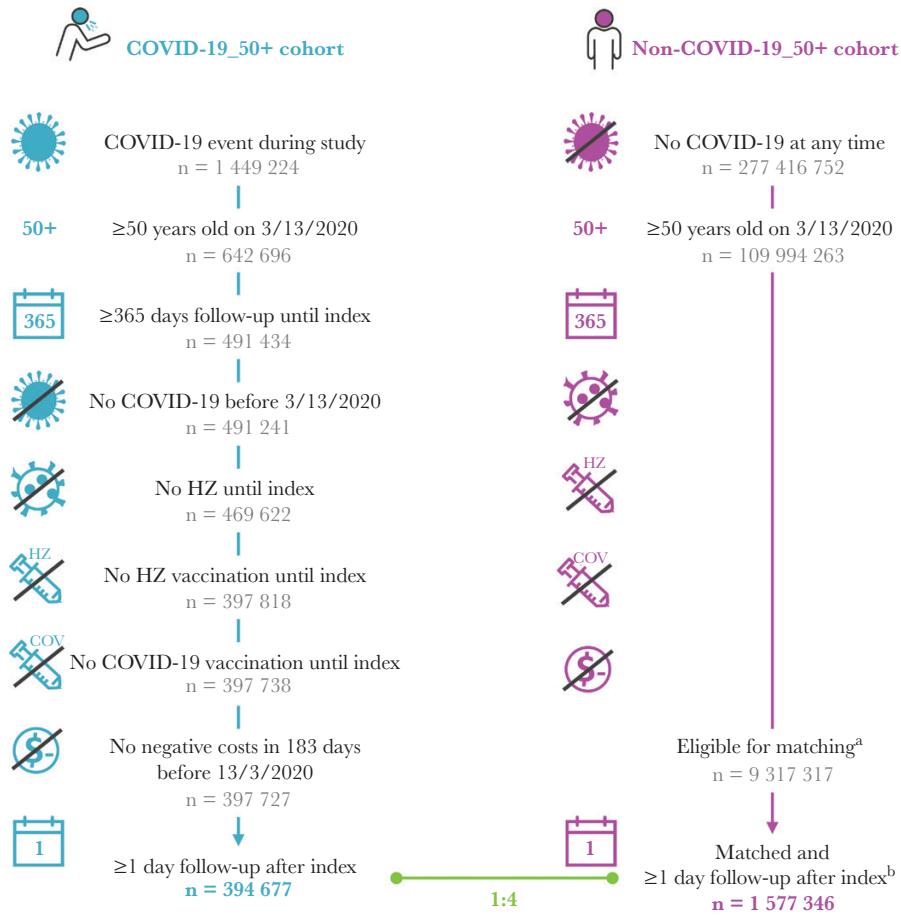


Figure 1. Disposition of individuals in the COVID-19_50+ and non-COVID-19_50+ cohorts. [a]Eligible for matching were those with ≥1 day of follow-up after March 13, 2020, and ≥365 days until March 13, 2020, no history of HZ, HZ vaccination, or COVID-19 vaccination until March 13, 2020, and no estimated negative total cost (in inpatient, outpatient, and pharmacy claims) during the 183 days before March 13, 2020. Further exclusions based on history of HZ, HZ vaccination, or COVID-19 vaccination until the index date were only done at the time of matching (when the index date was determined). [b]Four matches were identified for each individual with COVID-19, but not all had follow-up time beyond the index date; the latter were therefore not part of the matched non-COVID-19_50+ cohort. Abbreviations: COVID-19, coronavirus disease 2019; COVID-19_50+, cohort of individuals ≥50 years old with a first-time COVID-19 diagnosis during the study period; non-COVID-19_50+, cohort of individuals ≥50 years old with no history of COVID-19, clinically–epidemiologically diagnosed COVID-19, probable COVID-19, or suspected COVID-19 at any time, matched to individuals in the COVID-19_50+ cohort; HZ, herpes zoster; n, number of individuals remaining at the indicated step.

days in the COVID-19_50+ and 104.63 (81.94) days in the non-COVID-19_50+ cohort. Forty-one percent of COVID-19 diagnoses occurred in November and December 2020. Baseline characteristics were balanced between the 2 cohorts (SMD < 0.2) (Table 2), except for costs claimed for reimbursement during 1 year before the index date, which were higher in the COVID-19_50+ cohort (SMD = 0.22 for log[costs during 1 year before index + 1]) (Table 2).

A total of 78 050 (19.78%) patients from the COVID-19_50+ cohort were hospitalized with COVID-19 and were included in the analysis of HZ risk after COVID-19 hospitalization. Baseline characteristics for the hospitalized cohort and their matches are shown in Supplementary Table 1. The costs claimed for reimbursement during 1 year before the index date were higher among patients hospitalized with COVID-19 (SMD = 0.29 for log[costs during 1 year before index + 1]), as was the occurrence of diabetes any time before the index date (SMD = 0.23). The other baseline characteristics were balanced between cohorts.

Risk of HZ in Individuals With vs Without COVID-19

The crude HZ incidence rates per 1000 person-years were 8.16 (95% CI, 7.63–8.72) in ≥50-year-olds diagnosed with COVID-19 and 6.81 (95% CI, 6.57–7.05) in their matches without COVID-19 (Table 3). Poisson regression (adjusted for age, sex, and log[costs during 1 year before index + 1]) showed that ≥50-year-olds diagnosed with COVID-19 had a 15% higher risk of developing HZ than those without COVID-19 (aIRR, 1.15; 95% CI, 1.07–1.24; $P < .001$) (Figure 2). Our model also showed an increased risk of HZ (independent of COVID-19) in women vs men, in persons aged ≥65 years vs 50–64 years, and in those with higher health care costs (Supplementary Table 2). The increased risk of

Table 2. Baseline Characteristics for the COVID-19_50+ and Matched Non-COVID-19_50+ Cohorts

Characteristic	COVID-19_50+ (n = 394 677)	Non-COVID-19_50+ (n = 1 577 346)	SMD
Database, No. (%)			0.00
MarketScan	157 061 (39.79)	627 122 (39.76)	
Optum	237 616 (60.21)	950 224 (60.24)	
Mean age ± SD, y	64.84 ± 11.64	64.86 ± 11.47	0.00
Age group, No. (%)			0.00
50–64 y	232 157 (58.82)	927 422 (58.8)	
≥65 y	162 520 (41.18)	649 924 (41.2)	
Sex, No. (%)			0.00
Female	212 805 (53.92)	850 491 (53.92)	
Male	181 872 (46.08)	726 855 (46.08)	
≥1 immunocompromised condition or risk factor before index date, No. (%)	251 109 (63.62)	979 735 (62.11)	0.03
≥1 immunocompromised condition before index date, No. (%)	80 817 (20.48)	306 290 (19.42)	0.03
≥1 risk factor before index date, No. (%)	229 365 (58.11)	881 909 (55.91)	0.04
Risk factors before index date, No. (%)			
Rheumatoid arthritis	12 575 (3.19)	47 370 (3.00)	0.01
Inflammatory bowel disease	5012 (1.27)	22 195 (1.41)	0.01
Chronic obstructive pulmonary disease	66 487 (16.85)	251 080 (15.92)	0.03
Asthma	34 362 (8.71)	128 442 (8.14)	0.02
Chronic kidney disease	47 068 (11.93)	166 153 (10.53)	0.05
Depression[a]	74 176 (18.79)	238 085 (15.09)	0.10
Diabetes	149 344 (37.84)	523 254 (33.17)	0.10
Mean costs during 1 y before index ± SD, US$	64 187.27 ± 235 350.6	42 201.82 ± 158 474.78	0.12
Mean log(costs during 1 y before index + 1) ± SD	8.99 ± 2.29	8.37 ± 2.88	0.22

Abbreviations: COVID-19, coronavirus disease 2019; COVID-19_50+, cohort of individuals ≥50 years old with a first-time COVID-19 diagnosis during the study period; non-COVID-19_50+, cohort of individuals ≥50 years old with no history of COVID-19, clinically–epidemiologically diagnosed COVID-19, probable COVID-19, or suspected COVID-19 at any time, matched to individuals in the COVID-19_50+ cohort; SMD, standardized mean difference.

[a]Within 1 year before the index date.

HZ in ≥50-year-olds with COVID-19 was observed during the first 6 months after COVID-19 diagnosis, with statistically significant aIRR estimates during days 1–30 and days 91–183 and a nonsignificant aIRR during days 31–90. No increased HZ risk was seen in COVID-19 patients after day 183 (Table 3, Figure 2). When analyzing the HZ risk by age group, an increased risk of developing HZ was observed following COVID-19 diagnosis among 50–64-year-olds and ≥65-year-olds, although the increased risk in the latter group was not statistically significant (Table 3, Figure 2).

Table 3. HZ incidence Rates in Individuals Diagnosed With COVID-19 and Those Never Diagnosed With COVID-19

	COVID-19 Cohorts				Non-COVID-19 Cohorts			
Analysis	No. of Individuals	Days at Risk	No. of HZ Cases	Crude IR per 1000 PY (95% CI)	No. of Individuals	Days at Risk	No. of HZ Cases	Crude IR per 1000 PY (95% CI)
Overall, ≥50 y	394 677	39 012 531	872	8.16 (7.63–8.72)	1 577 346	165 043 695	3077	6.81 (6.57–7.05)
Hospitalized, ≥50 y	78 050	7 104 711	197	10.13 (8.77–11.64)	312 055	35 838 002	779	7.94 (7.39–8.51)
Days 1–30,[a] ≥50 y	394 677	10 541 107	248	8.59 (7.56–9.73)	1 577 346	42 802 543	793	6.77 (6.31–7.25)
Days 31–90,[a] ≥50 y	303 760	13 707 247	304	8.10 (7.22–9.06)	1 257 148	57 814 728	1105	6.98 (6.58–7.40)
Days 91–183,[a] ≥50 y	165 483	10 847 688	263	8.86 (7.82–9.99)	710 816	47 150 431	858	6.65 (6.21–7.10)
Days >183,[a] ≥50 y	70 986	3 916 489	57	5.32 (4.03–6.88)	312 049	17 275 993	321	6.79 (6.07–7.57)
50–64 y	232 157	24 430 573	480	7.18 (6.55–7.85)	927 422	97 072 577	1549	5.83 (5.54–6.13)
≥65 y	162 520	14 581 958	392	9.82 (8.87–10.84)	649 924	67 971 118	1528	8.21 (7.81–8.63)

Abbreviations: COVID-19, coronavirus disease 2019; COVID-19 cohorts, cohorts of individuals of the indicated ages with a first-time COVID-19 diagnosis during the study period and, for "hospitalized," with a COVID-19-associated inpatient claim within 21 days of the first COVID-19 diagnosis; HZ, herpes zoster; IR, incidence rate; non-COVID-19 cohorts, cohorts of individuals of the indicated ages with no history of COVID-19, clinically–epidemiologically diagnosed COVID-19, probable COVID-19, or suspected COVID-19 at any time, matched to individuals in the corresponding COVID-19 cohorts; PY, person-years.

[a]Time after the index date.

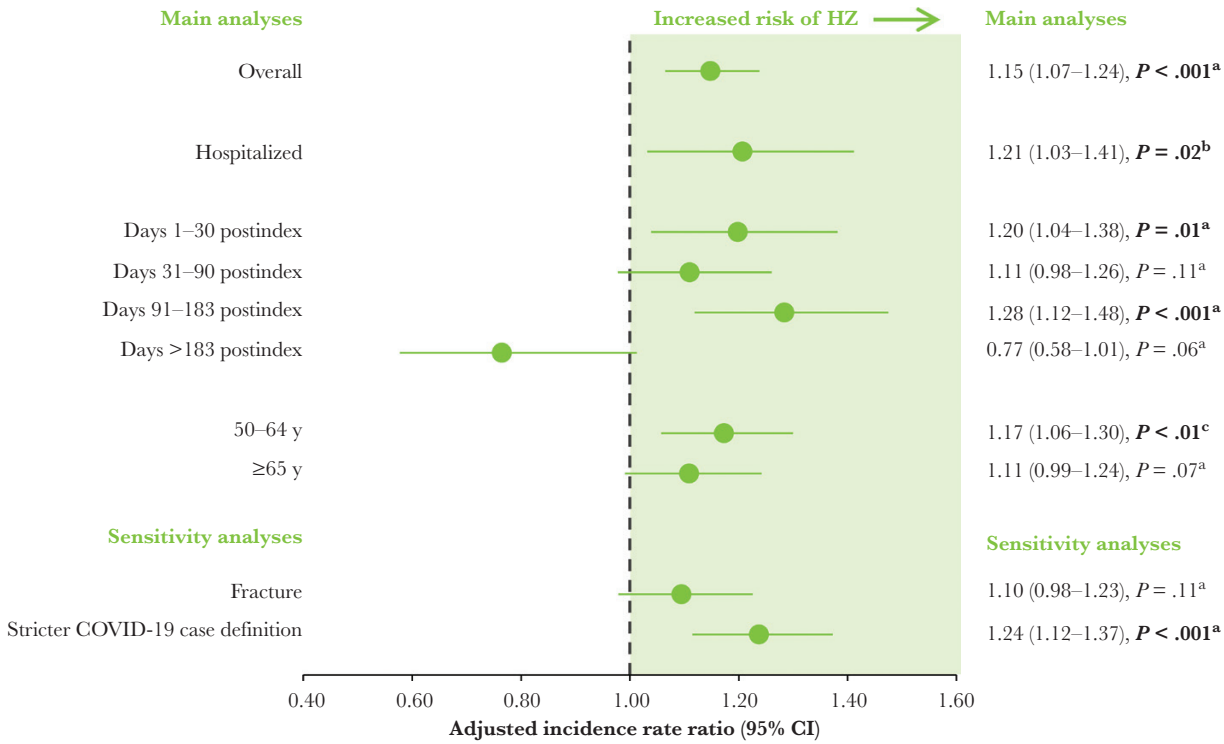


Figure 2. Relative risk of HZ in individuals diagnosed with COVID-19 vs those never diagnosed with COVID-19 (or with vs without fractures). Bold formatting indicates statistical significance. All analyses were on individuals ≥50 years old diagnosed with COVID-19 vs those never diagnosed with COVID-19, unless when otherwise stated. [a]Adjusted for sex, age category, and log(cost during 1 year before index + 1). For the sensitivity analysis on fractures, the standardized mean difference for log(cost during 1 year before index + 1) between the fracture and nonfracture cohorts was just below 0.20, but the variable was still included in the model for consistency with the main analyses. [b]Adjusted for sex and log(cost during 1 year before index + 1). Diabetes before the index date and diabetes before March 13, 2020, were considered for inclusion in the model because of an observed imbalance but were discarded due to nonsignificant effects. [c]Adjusted for sex, log(cost during 1 year before index + 1), and interaction between cohort and age category. Analysis was produced based on the population ≥18 years old. Abbreviations: COVID-19, coronavirus disease 2019; days, days after the index date; HZ, herpes zoster.

When we used a more specific case definition for COVID-19 diagnosis (which resulted in a cohort of 177 503 individuals with COVID-19 and a cohort of 709 527 matched controls), the aIRR of the HZ incidence in ≥50-year-olds with vs without COVID-19 was 1.24 (95% CI, 1.12–1.37; $P < .001$) (Figure 2, sensitivity analysis). Of note, with this case definition, the proportion of individuals with COVID-19 who were hospitalized was higher (43.97%) than with the case definition for the main analysis (19.78%).

The crude HZ incidence in ≥50-year-old patients who had been hospitalized with COVID-19 was 10.13 (95% CI, 8.77–11.64) per 1000 person-years, compared with 7.94 (7.39–8.51) per 1000 person-years in their matches (Table 3). Patients hospitalized with COVID-19 had a 21% higher risk of developing HZ than those never diagnosed with COVID-19 (aIRR, 1.21; 95% CI, 1.03–1.41; $P = .02$) (Figure 2).

Sensitivity Analysis of HZ Risk in Individuals With vs Without Fractures

For the sensitivity analysis using fractures as exposure, 123 141 individuals age ≥50 years with arm, leg, hand, or foot fractures were matched to 492 270 individuals without fractures with ≥1 day of follow-up. The mean (SD) follow-up time after the index date was similar in both cohorts (139.28 ± 85.87 days vs 143.46 ± 85.42 days), and baseline characteristics were balanced between cohorts, except log(costs during 1 year before index + 1; SMD = 0.20) (Supplementary Table 3). No statistically significant difference in HZ incidence was observed between ≥50-year-olds with and without fractures: the crude incidence rates were 8.28 (95% CI, 7.48–9.15) and 7.21 (95% CI, 6.83–7.59) per 1000 person-years, respectively, and the aIRR was 1.10 (95% CI, 0.98–1.23; $P = .11$) (Figure 2).

DISCUSSION

Previous case reports, case series, and descriptive analyses have suggested a possible association between COVID-19 and HZ [7–9, 20–23]. However, as these types of studies provide low-grade evidence for an association, it has not previously been possible to determine whether patients with COVID-19 have a higher risk of developing HZ. To our knowledge, our study is the first large, retrospective cohort study designed to investigate the hypothesis that COVID-19 could increase the risk of HZ. We found that during the first year of the COVID-19 pandemic, ≥50-year-old individuals with a first-time COVID-19 diagnosis had a significantly higher risk of developing HZ than those never

diagnosed with COVID-19. Maintaining latency of VZV after initial infection requires sufficient levels of VZV-specific T-cell immunity, and declines in cell-mediated immunity (eg, in older people due to immunosenescence or under immunosuppressing conditions) can trigger VZV reactivation and lead to HZ [2, 4]. As SARS-CoV-2 infection can result in T-cell immune dysfunction, it was previously hypothesized that this could trigger latent VZV reactivation [7, 20]. Several studies have shown that a large proportion of COVID-19 patients present with lymphopenia [10–12, 24], with significantly lower counts of total lymphocytes, CD4+ T cells, CD8+ T cells, B cells, and natural killer cells in COVID-19 patients compared with healthy controls [12]. Some studies have also suggested that SARS-CoV-2 infection may impair CD4+ helper and regulatory T-cell function and cause hyperactivation of CD8+ T cells, followed by their exhaustion [10, 14]. Lymphopenia has been shown to be more pronounced in severe COVID-19 cases [10–12, 24]. In line with this, we found a greater increase in the HZ risk when selecting for potentially more severe cases of COVID-19: the risk of developing HZ was 15% higher in individuals diagnosed with COVID-19, 24% higher when using a more specific case definition (requiring either 1 inpatient or 2 outpatient claims, hence selecting for a higher proportion of hospitalized patients), and 21% higher in patients hospitalized with COVID-19.

In the published case reports and case series, more than half of the described HZ cases occurred within 1 week after COVID-19 diagnosis or hospitalization, but some cases were also reported after 8–10 weeks [7]. This is consistent with the results of the present study, in which an increased risk was observed up to 6 months after COVID-19 diagnosis. No increased risk of developing HZ was seen beyond 6 months after COVID-19 diagnosis in our study, which may indicate a recovery of cell-mediated immunity. However, caution is warranted when interpreting these results as the number of individuals with a follow-up time >6 months was lower than for the other assessed time intervals.

In our analyses by age, we found an increased HZ risk in 50–64-year-olds and in ≥65-year-olds. The latter was not statistically significant, but this may be due to the smaller sample size of this age group, not compensated by the relatively high HZ incidence due to older age; our study was not powered to assess the association between COVID-19 and HZ in the different age subgroups.

Our study has several strengths. We used data from 2 large US databases and matched persons with and without COVID-19 by various known HZ risk factors. Moreover, to calculate the IRRs, we used a Poisson regression model to adjust any variables that showed an imbalance between the COVID-19 and non-COVID-19 cohorts despite matching, thereby further controlling for possible confounding. Our model identified older age and female sex as independent risk factors for HZ, confirming its validity, as age and sex are known HZ risk factors [2, 4]. The sensitivity analysis on individuals with vs without fractures indicated no significantly different HZ incidence between these 2 groups, suggesting that the effect of COVID-19 on HZ was due to COVID-19 rather than other factors. Although HZ cases were not laboratory-confirmed, our definition to identify HZ cases was more specific than that often used in other studies: 1 inpatient claim or 2 outpatient claims within 30 days or 1 outpatient claim and a pharmacy claim (in our study) compared with a single claim with HZ diagnosis (in other studies [25, 26]). The latter was shown to have a positive predictive value (PPV) of 85%–100% [27], meaning that our definition also had a very high PPV.

The limitations of our study include those inherent to retrospective research based on claims data. The 2 databases do not contain information from individuals insured through Medicaid or Medicare (other than Medicare Advantage). As the rates of these public insurance plans are high in certain economically disadvantaged and racial/ethnic groups, the results of our study may not be generalizable. Even though our study design controlled for possible confounding, there may have been other factors that contributed to (or diminished) the observed HZ risk. For instance, the MarketScan and Optum databases contain no information on race and ethnicity. As COVID-19 has disproportionately affected the African American population [28, 29], the COVID-19 cohort in our study may include proportionately more African Americans than the non-COVID-19 cohort. This may have led to an underestimation of the effect of COVID-19 on HZ, given that Black individuals have a lower risk of HZ than White individuals [4, 30]. Some COVID-19 and HZ cases may have been missed, although for HZ, no differential rate of missed cases is expected between cohorts. If COVID-19 cases were missed (either because they were asymptomatic or mild and therefore not tested—which may have been especially the case in the early months of the pandemic when testing capacity was limited—or because their tests were not recorded in the database), individuals with COVID-19 might have been assigned to the non-COVID-19 cohort, which could have influenced the estimated IRRs. We could also not determine the sensitivity and specificity of the COVID-19 diagnoses. However, we did not include claims with the ICD-10 code for clinically–epidemiologically diagnosed, probable, or suspected COVID-19 (virus not identified) in the COVID-19 cohort, and we believe that the codes used to identify COVID-19 patients were more specific to laboratory-confirmed COVID-19. While we excluded HZ- and COVID-19-vaccinated persons, it is possible that not all vaccinations were recorded in the database. Missed COVID-19 vaccinations would likely not have impacted the results, as the study mostly covered the period before COVID-19 mass vaccination.

In conclusion, our results indicate that ≥50-year-olds diagnosed with COVID-19 have a significantly higher risk of developing HZ, suggesting that SARS-CoV-2 infection may trigger reactivation of latent VZV. Health care professionals should

consider that COVID-19 may be a risk factor for HZ. As HZ is a vaccine-preventable disease, maintaining recommended HZ vaccination in ≥50-year-olds may help reduce the HZ burden during the pandemic.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Acknowledgments

The authors are grateful to Jasur Danier for his contributions to the study design. They also thank Modis for medical writing support (provided by Natalie Denef), graphic design (provided by Ioana Cristina Ilea), and manuscript coordination (provided by Julie Mellery), on behalf of GSK.

Financial support. This work was supported by GlaxoSmithKline Biologicals S.A. GlaxoSmithKline Biologicals S.A. was involved in all stages of the study conduct and analysis and covered all costs associated with the development and publishing of this manuscript.

Potential conflicts of interest. A.B., C.W., R.P., Y.B., N.S., M.S., R.W., and E.A. are employees of the GSK group of companies. A.B., C.W., R.P., R.W., and E.A. hold shares in the GSK group of companies as part of their employee remuneration. G.L. is employed by Business & Decision Life Sciences, and K.C. is employed by Aixial, an Alten Company, both working on behalf of the GSK group of companies. All authors declare no other financial or nonfinancial relationships and activities. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

Author contributions. A.B., G.L., C.W., K.C., R.P., N.S., M.S., R.W., and E.A. were involved in the conception or design of the study. G.L., C.W., K.C., Y.B., N.S., and E.A. participated in the collection or generation of the study data. A.B., G.L., C.W., K.C., R.P., Y.B., N.S., and E.A. performed the study. A.B., G.L., C.W., K.C., Y.B., N.S., M.S., and R.W. contributed to the study with materials or analysis tools. All authors were involved in the analyses or interpretation of the data, reviewed and revised the manuscript, and approved the final manuscript as submitted. All authors had full access to all study data and take responsibility for the integrity of the data and the accuracy of the data analysis.

Prior presentations. The results of this study were presented at the 17th European Union Geriatric Medicine Society (EuGMS) Congress, 11–13 October 2021, Athens, Greece, and virtual; and at the 2021 Canadian Immunization Conference, 8–9 December 2021, virtual.

Data availability. Study documents can be requested for further research from www.clinicalstudydatarequest.com.

Patient consent. This study was conducted in accordance with the ethical principles derived from the Declaration of Helsinki and the Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines, the Food and Drug Administration Code of Federal Regulations Title 21 (21 CFR), and all other applicable regulations and local laws. The study was reviewed by GSK's Clinical Health Economics Regulatory Modeling and Epidemiology review board. As GSK owns a license to analyze the MarketScan and Optum databases and these databases are both pseudonymized and fully compliant with the Health Insurance Portability and Accountability Act, no additional ethics committee approval was needed for this research. Patient consent was not needed for this type of study.

References

1. Cohen JI. Clinical practice: herpes zoster. N Engl J Med **2013**; 369:255–63.
2. Gershon AA, Gershon MD, Breuer J, Levin MJ, Oaklander AL, Griffiths PD. Advances in the understanding of the pathogenesis and epidemiology of herpes zoster. J Clin Virol **2010**; 48:S2–7.
3. Kawai K, Gebremeskel BG, Acosta CJ. Systematic review of incidence and complications of herpes zoster: towards a global perspective. BMJ Open **2014**; 4:e004833.
4. Marra F, Parhar K, Huang B, Vadlamudi N. Risk factors for herpes zoster infection: a meta-analysis. Open Forum Infect Dis **2020**; 7:ofaa005.
5. McKay SL, Guo A, Pergam SA, Dooling K. Herpes zoster risk in immunocompromised adults in the United States: a systematic review. Clin Infect Dis **2020**; 71:e125–34.
6. World Health Organization. Listings of WHO's response to COVID-19. Available at: https://www.who.int/news/item/29-06-2020-covidtimeline. Accessed 18 October 2021.
7. Diez-Domingo J, Parikh R, Bhavsar AB, Cisneros E, McCormick N, Lecrenier N. Can COVID-19 increase the risk of herpes zoster? A narrative review. Dermatol Ther (Heidelb) **2021**; 11:1119–26.
8. Maia CMF, Marques NP, de Lucena EHG, de Rezende LF, Martelli DRB, Martelli-Júnior H. Increased number of herpes zoster cases in Brazil related to the COVID-19 pandemic. Int J Infect Dis **2021**; 104:732–3.
9. Ertugrul G, Aktas H. Herpes zoster cases increased during COVID-19 outbreak. Is it possible a relation? J Dermatolog Treat **2020**; 1.
10. Terpos E, Ntanasis-Stathopoulos I, Elalamy I, et al. Hematological findings and complications of COVID-19. Am J Hematol **2020**; 95:834–47.
11. Debuc B, Smadja DM. Is COVID-19 a new hematologic disease? Stem Cell Rev Rep **2021**; 17:4–8.
12. Wang F, Nie J, Wang H, et al. Characteristics of peripheral lymphocyte subset alteration in COVID-19 pneumonia. J Infect Dis **2020**; 221:1762–9.
13. Bobcakova A, Petriskova J, Vysehradsky R, et al. Immune profile in patients with COVID-19: lymphocytes exhaustion markers in relationship to clinical outcome. Front Cell Infect Microbiol **2021**; 11:646688.
14. Zheng HY, Zhang M, Yang CX, et al. Elevated exhaustion levels and reduced functional diversity of T cells in peripheral blood may predict severe progression in COVID-19 patients. Cell Mol Immunol **2020**; 17:541–3.
15. Centers for Disease Control and Prevention. COVID-19 information for specific groups of people. Available at: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/index.html. Accessed 18 October 2021.
16. Centers for Disease Control and Prevention. Risk for COVID-19 infection, hospitalization, and death by age group. Available at: https://www.cdc.gov/coronavirus/2019-ncov/covid-data/investigations-discovery/hospitalization-death-by-age.html. Accessed 18 October 2021.
17. IBM Watson Health. IBM MarketScan Research Databases for life sciences researchers. Available at: https://www.ibm.com/downloads/cas/OWZWJ0QO. Accessed 18 October 2021.
18. Boëlle PY, Delory T, Maynadier X, et al. Trajectories of hospitalization in COVID-19 patients: an observational study in France. J Clin Med **2020**; 9:3148.
19. Faes C, Abrams S, Van Beckhoven D, Meyfroidt G, Vlieghe E, Hens N. Time between symptom onset, hospitalisation and recovery or death: statistical analysis of Belgian COVID-19 patients. Int J Environ Res Public Health **2020**; 17:7560.
20. Wang B, Guo S, Yao Y, Li Y, Zhang G. Dermatologists may need to pay more attention to herpes zoster during the pandemic of COVID-19. Infect Dis (Lond) **2020**; 52:917–8.
21. Brambilla L, Maronese CA, Tourlaki A, Veraldi S. Herpes zoster following COVID-19: a report of three cases. Eur J Dermatol **2020**; 30:754–6.
22. Voisin O, Deluca N, Mahé A, et al. Disseminated herpes zoster during COVID-19. Infect Dis Clin Pract (Baltim Md) **2021**; 29:e109–10.
23. Ghosh B, Gajjar RA, Modi VK, Jadeja DM. A rare case of herpes zoster in an adult patient recovered from symptomatic reinfection of COVID-19. Cureus **2021**; 13:e16274.
24. Guan WJ, Ni ZY, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med **2020**; 382:1708–20.
25. Insinga RP, Itzler RF, Pellissier JM, Saddier P, Nikas AA. The incidence of herpes zoster in a United States administrative database. J Gen Intern Med **2005**; 20:748–53.
26. Leung J, Harpaz R, Molinari NA, Jumaan A, Zhou F. Herpes zoster incidence among insured persons in the United States, 1993-2006: evaluation of impact of varicella vaccination. Clin Infect Dis **2011**; 52:332–40.
27. Zhang J, Xie F, Delzell E, et al. Association between vaccination for herpes zoster and risk of herpes zoster infection among older patients with selected immune-mediated diseases. JAMA **2012**; 308:43–9.
28. Centers for Disease Control and Prevention. Risk for COVID-19 infection, hospitalization, and death by race/ethnicity. Available at: https://www.cdc.gov/coronavirus/2019-ncov/covid-data/investigations-discovery/hospitalization-death-by-race-ethnicity.html. Accessed 18 October 2021.
29. Vasquez Reyes M. The disproportional impact of COVID-19 on African Americans. Health Hum Rights **2020**; 22:299–307.
30. Kawai K, Yawn BP. Risk factors for herpes zoster: a systematic review and meta-analysis. Mayo Clin Proc **2017**; 92:1806–21.