Correspondence

Clinical Letter

No evidence for an increased risk of herpes zoster requiring full or partial hospitalization during the first year of the COVID-19 pandemic in Germany

Dear Editors,

herpes zoster (HZ) is a common viral disease caused by reactivation of varicella zoster virus following a decline in cell-mediated immunity [1]. COVID-19 is associated with significant T-cell immune dysfunction, and increased rates of HZ in COVID-19 patients have been recently reported in the literature [2, 3]. These findings encouraged us to evaluate changes of HZ-incidences during the first year of the COVID-19 pandemic in Germany.

We performed a retrospective analysis of claims data from all Helios hospitals in Germany. The Helios hospital group operates metropolitan and regional acute care hospitals ranging from basic to maximum care, outpatient clinics, and prevention centers throughout Germany (https://www.helios-gesundheit.de/). The 89 Helios hospitals provide care for up to 1.2 million inpatients annually, corresponding to a total of 7% of all hospitalizations in Germany. All ongoing HZ cases with a hospital admission (including partial hospitalization) between March 2020 and April 2021 (target-period) were analyzed and compared to a corresponding control-period (March 2016 to February 2020). Hospitalizations were selected based on the main discharge diagnosis of HZ (B02), according to the International Statistical Classification of Diseases and Related Health Problems (ICD-10-GM [German Modification]).

For statistical analyses, inferential statistics for count data were based on Poisson mixed models using hospitals as random factor in the R software program [4, 5]. We report crude-risk ratios (calculated by exponentiation of the regression coefficients) together with 95% confidence intervals and P values. To describe patient characteristics of both cohorts, we employed χ²-tests for binary variables and analysis of variance for numeric variables. For relative-risk analysis, Poisson regression was used. Length of hospital stay was analyzed with a linear mixed model. We log-transformed length of stay because of its right-skewed distribution. For all tests we applied a two-tailed 5% error criterion for significance.

This study was approved by the Ethics Committee at the Medical Faculty of Leipzig University (#490/20-ek).

Overall, there were 4,487 cases of HZ with hospital admissions between March 2020 and April 2021 as opposed to 18,487 HZ cases in the period from March 2016 to February 2020 (Figure 1). With the beginning of 2020, a lower HZ hospitalization rate was observed, most likely related to the first COVID-19 pandemic wave. In total, the rate of daily HZ hospitalizations did not increase during the target period (10.9 vs. 12.7 in the control period; crude-risk-ratio: 0.86, 95% CI 0.83–0.89, P < 0.01). The incidence rate (per 100,000) did not increase (daily median of 133 vs. 118 in the control period), nor did the relative risk of HZ development

Figure 1 Total weekly hospital admissions for herpes zoster at 89 Helios hospitals in Germany during the first year of the COVID-19 pandemic. The shaded areas represent 95% confidence intervals (CI). The boxplot represents the distribution of weekly case numbers in the control period. The bold bar indicates the median; the box ranges from the first to the third quartile. The lines extend 1.5 interquartile ranges from the box. Outliers are indicated by grey circles.
Table 1  Comparison of patients characteristics of both patient cohorts.

| Proportion (n)                              | Control period | Target period | P value |
|--------------------------------------------|----------------|---------------|---------|
| **Group**                                  |                |               |         |
| **Age**                                    |                |               |         |
| Mean (SD)                                  | 65.6 ± 19.2    | 66.5 ± 18.1   | < 0.01  |
| ≤ 59 years                                 | 31.0 % (5,737) | 29.9 % (3,143) | 0.16    |
| 60–69 years                                | 17.2 % (3,181) | 18.2 % (815)  | 0.13    |
| 70–79 years                                | 26.3 % (4,867) | 22.9 % (1,029) | < 0.01  |
| ≥ 80 years                                 | 25.4 % (4,702) | 29.0 % (1,300) | < 0.01  |
| **Sex**                                    |                |               |         |
| Male                                       | 41.7 % (7,711) | 43.2 % (1,938) | 0.07    |
| Female                                     | 58.3 % (10,776) | 56.8 % (2,549) |         |
| **Elixhauser comorbidity index**           |                |               |         |
| Mean (SD)                                  | 5.1 ± 9.5      | 5.0 ± 9.5     | 0.69    |
| < 0                                         | 15.9 % (2,940) | 16.8 % (755)  | 0.14    |
| o                                           | 42.7 % (7,886) | 43.3 % (1,943) | 0.44    |
| 1–4                                        | 5.3 % (988)    | 4.6 % (208)   | 0.06    |
| ≥ 5                                        | 36.1 % (6,673) | 35.2 % (1,581) | 0.29    |
| **Congestive heart failure**               |                |               |         |
| No                                         | 88.7 % (16,403) | 88.3 % (3,964) |         |
| Yes                                        | 11.3 % (2,084) | 11.7 % (523)  | 0.48    |
| **Cardiac arrhythmias**                    |                |               |         |
| No                                         | 86.5 % (15,983) | 85.8 % (3,850) |         |
| Yes                                        | 13.5 % (2,504) | 14.2 % (637)  | 0.26    |
| **Valvular heart disease**                 |                |               |         |
| No                                         | 95.3 % (17,612) | 95.3 % (4,275) |         |
| yes                                        | 4.7 % (875)    | 4.7 % (212)   | 1.00    |
| **Pulmonary circulation disorders**        |                |               |         |
| No                                         | 97.9 % (18,108) | 97.8 % (4,390) |         |
| Yes                                        | 2.1 % (379)    | 2.2 % (97)    | 0.68    |
| **Peripheral vascular disorders**          |                |               |         |
| No                                         | 95.1 % (17,587) | 95.9 % (4,303) |         |
| Yes                                        | 4.9 % (900)    | 4.1 % (184)   | 0.03    |
| **Arterial hypertension (uncomplicated)**  |                |               |         |
| No                                         | 67.3 % (12,439) | 66.6 % (2,987) |         |
| Yes                                        | 32.7 % (6,048) | 33.4 % (1,500) | 0.37    |
| **Arterial hypertension (complicated)**    |                |               |         |
| No                                         | 92.6 % (17,122) | 93.2 % (4,181) |         |
| Yes                                        | 7.4 % (1,365)  | 6.8 % (306)   | 0.20    |
| **Paralysis**                              |                |               |         |
| No                                         | 97.5 % (18,018) | 97.7 % (4,385) |         |
| yes                                        | 2.5 % (469)    | 2.3 % (102)   | 0.33    |

Continued
### Table 1

| Group                              | Control period | Target period | \( P \) value |
|------------------------------------|----------------|---------------|---------------|
| **Neurological disorders**         |                |               |               |
| No                                 | 95.8 % (17,710) | 95.7 % (4,292) | 0.70          |
| Yes                                | 4.2 % (777)    | 4.3 % (195)   |               |
| **Chronic pulmonary disease**      |                |               |               |
| No                                 | 92.7 % (17,138) | 93.8 % (4,209) | 0.01          |
| Yes                                | 7.3 % (1,349)  | 6.2 % (278)   |               |
| **Diabetes mellitus (uncomplicated)** |            |               |               |
| No                                 | 91.0 % (16,830) | 90.7 % (4,070) | 0.51          |
| Yes                                | 9.0 % (1,657)  | 9.3 % (417)   |               |
| **Diabetes mellitus (complicated)** |            |               |               |
| No                                 | 94.1 % (17,404) | 94.1 % (4,224) | 1.00          |
| Yes                                | 5.9 % (1,083)  | 5.9 % (263)   |               |
| **Hypothyroidism**                 |                |               |               |
| No                                 | 91.3 % (16,875) | 90.2 % (4,048) | 0.03          |
| Yes                                | 8.7 % (1,612)  | 9.8 % (439)   |               |
| **Renal failure**                  |                |               |               |
| No                                 | 77.3 % (14,296) | 78.2 % (3,508) | 0.23          |
| Yes                                | 22.7 % (4,191) | 21.8 % (979)  |               |
| **Liver disease**                  |                |               |               |
| No                                 | 97.0 % (17,927) | 97.4 % (4,369) | 0.17          |
| Yes                                | 3.0 % (360)    | 2.6 % (118)   |               |
| **Peptic ulcer disease (excluding bleeding)** | |               |               |
| No                                 | 99.9 % (18,470) | 99.9 % (4,484) | 0.82          |
| Yes                                | 0.1 % (17)     | 0.1 % (3)     |               |
| **AIDS/HIV**                       |                |               |               |
| No                                 | 99.9 % (18,468) | 99.9 % (4,481) | 0.76          |
| Yes                                | 0.1 % (19)     | 0.1 % (6)     |               |
| **Malignant hematological diseases/lymphoma** | |               |               |
| No                                 | 97.9 % (18,096) | 98.1 % (4,401) | 0.44          |
| Yes                                | 2.1 % (391)    | 1.9 % (86)    |               |
| **Metastatic cancer (all entities)** |            |               |               |
| No                                 | 97.8 % (18,072) | 97.8 % (4,389) | 0.85          |
| Yes                                | 2.2 % (415)    | 2.2 % (98)    |               |
| **Solid tumor (without metastasis)** |            |               |               |
| No                                 | 95.4 % (17,638) | 95.9 % (4,304) | 0.15          |
| Yes                                | 4.6 % (849)    | 4.1 % (183)   |               |
Table 1 Continued.

| Proportion (n) | Control period | Target period | P value |
|----------------|----------------|---------------|---------|
| **Group**      |                |               |         |
| Rheumatoid arthritis/connective tissue diseases | | | |
| No             | 97.3 % (17,985)| 97.3 % (4,365)| 1.00    |
| Yes            | 2.7 % (502)    | 2.7 % (122)   |         |
| Coagulopathy   |                |               |         |
| No             | 97.6 % (18,049)| 97.8 % (4,388)|         |
| Yes            | 2.4 % (438)    | 2.2 % (99)    | 0.55    |
| Obesity        |                |               |         |
| No             | 91.5 % (16,907)| 91.7 % (4,114)|         |
| Yes            | 8.5 % (1,580)  | 8.3 % (373)   | 0.64    |
| Weight loss/kachexia | | | |
| No             | 94.9 % (17,545)| 95.7 % (4,294)|         |
| Yes            | 5.1 % (942)    | 4.3 % (193)   | 0.03    |
| Fluid and electrolyte disorders | | | |
| No             | 84.7 % (15,657)| 83.4 % (3,741)|         |
| Yes            | 15.3 % (2,830) | 16.6 % (746)  | 0.03    |
| Anemia (due to blood loss) | | | |
| No             | 99.7 % (18,426)| 99.8 % (4,477)|         |
| Yes            | 0.3 % (61)     | 0.2 % (10)    | 0.31    |
| Iron deficiency anemia | | | |
| No             | 98.2 % (18,162)| 98.5 % (4,419)|         |
| Yes            | 1.8 % (325)    | 1.5 % (68)    | 0.29    |
| Alcoholism/alcohol abuse | | | |
| No             | 99.2 % (18,330)| 99.0 % (4,441)|         |
| Yes            | 0.8 % (157)    | 1.0 % (46)    | 0.30    |
| Drug abuse     |                |               |         |
| No             | 99.4 % (18,378)| 99.6 % (4,468)|         |
| Yes            | 0.6 % (109)    | 0.4 % (19)    | 0.22    |
| Psychoses      |                |               |         |
| No             | 99.7 % (18,435)| 99.7 % (4,473)|         |
| Yes            | 0.3 % (52)     | 0.3 % (14)    | 0.85    |
| Depression     |                |               |         |
| No             | 94.0 % (17,385)| 94.1 % (4,222)|         |
| Yes            | 6.0 % (1,102)  | 5.9 % (265)   | 0.92    |
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compared to the control group (relative risk: 0.89, 95 % CI 0.87–0.92, P < 0.01). The length of hospital stays in HZ patients significantly decreased during the first year of the COVID-19 pandemic (6.9 ± 12.0 days in the control period vs. 5.9 ± 8.3 days [mean and SD] in the target period; P < 0.01). Age, sex, and comorbidities were comparable between target period and control period. All patient characteristics are summarized in Table 1. Overall, daily hospital admissions in the 12 dermatology departments of the Helios hospital groups decreased by 9.54 % (162.1 vs. 179.2 in the control period; crude-risk-ratio: 0.90, 95 % CI 0.90–0.91, P < 0.01) during the evaluated time period.

Recently, Maia et al. reported an increased incidence of HZ in Brazil during the COVID-19 pandemic [3]. Using data from the Unified Health System of five Brazilian regions, the authors compared the number of HZ diagnoses during the first months of the COVID-19 pandemic (March to August 2020) to similar time-periods (March – August) in the years 2017–2019. As a key finding, an overall increase of HZ cases of 35.4 % per million inhabitants was observed, corresponding to an extra 10.7 HZ cases per million during the COVID-19 pandemic in all Brazilian regions. COVID-19-induced decreases in cell counts (especially CD4+, CD8+, B cells and natural killer cells) and SARS-CoV-2-associated immune dysregulation have been suggested as potential key factors involved in varicella zoster virus (VZV) reactivation. Based on the data source used (DATASUS of the Brazilian public health system), hospitalization status (full/partial hospitalization or out-patient care) is not available [3].

By analyzing data from the German-wide Helios hospital network, we have found no evidence for an increased risk of hospital admission due to HZ during the first year of the COVID-19 pandemic. An adjuvant HZ subunit (Shingrix) vaccine is recommended in adults older than 60 years by the German Standing Commission on Vaccination (STIKO, Ständige Impfkommission) since the end of 2018. As the current HZ vaccination rates in Germany are low (nationwide vaccination rate of 0.7 % in 2020), direct effects on the HZ incidences of this study are rather unlikely [6].

The results of this study should be interpreted in light of its limitations. A main limitation might be the fact that predominantly severe HZ (for example, facial HZ, older patients, or HZ in patients with immunosuppression) requiring full or partial hospitalization were included, and therefore our findings might not be generalizable. Moreover, due to the nature of data collection, we were unable to evaluate other potentially disease-causing factors, such as infections, UV-irradiation, drugs, or stress. As the hospital admission rates in Germany were 13 % lower in the year 2020 compared to previous years, we cannot exclude that a high number of patients with HZ may have withdrawn from inpatient treatment in favor of treatment on an outpatient basis [7]. Moreover, data on disease severity and complication rates are lacking in our study.

Interestingly, sporadic cases of HZ following mRNA vaccination with BNT162b2 in patients with rheumatic diseases have been recently reported [8]. In addition, a recent Spanish cross-sectional study evaluating cutaneous reactions after SARS-CoV-2 vaccination demonstrated high rates (13.8 %) of herpes simplex and VZV reactivation [9]. Although we did not see HZ increases since the beginning of vaccination against COVID-19 in early 2021, this important observation warrants further study.

Acknowledgement

Open access funding enabled and organized by Projekt DEAL.

Conflict of interest

None.

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