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The Characteristics of Hospitalized Patients with Herpes Zoster Over the Years

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Abstract

Introduction: Herpes Zoster (HZ) represents a significant health burden, most commonly affecting elderly and immunocompromised patients. In the recent years, increasing rates of HZ-related hospitalizations have been reported worldwide, particularly among patients with predisposing risk factors.

Objective: The objectives of the study aims were to estimate the hospitalization rates in Israel, to characterize the patients' clinical profile, as well as their disease course and prognosis.

Methods: A retrospective cohort study, using data from electronic medical records of patients hospitalized with HZ at Clalit Health Services' seven hospitals from January 2002 to December 2024. The data was evaluated for: the annual rate of hospitalizations, patients' demographic and the clinical characteristics, hospitalization course, complications and outcome.

Results: The cohort included 3,907 patients (mean age 68 ± 18 years; 52% women). Hospitalization rates ranged from 1.54 to 2.67 per 100,000, peaking in 2018 (n=237 per year) and declining thereafter. The majority of hospitalizations (57%) were at the two tertiary care centers. Common comorbidities included immunosuppressive therapy (49%), malignancy (43%), diabetes mellitus (39%) and organ transplant recipients (8%). Antiviral treatment by Acyclovir was administered in 96% of the cases, primarily intravenously (50%), for a mean of 6 ± 4 days. Complications occurred in 20%, most frequently post-herpetic neuralgia (7%). The 30-days mortality rate was 2% and re-hospitalization due to recurrence occurred in 0.84%.

Conclusions: HZ-related hospitalization rates fluctuated but showed no consistent upward trend throughout the study period. Several risk factors were identified, emphasizing early prevention through vaccination to reduce disease burden and complications.

Keywords: Herpes zoster; Hospitalization; Comorbidities; Complications; Mortality; Vaccination

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Introduction

Primary infection by Varicella Zoster Virus (VZV), typically occurring during childhood, often leads to acute varicella, after which the virus remains dormant in the ganglion cells. A reactivation may lead to Herpes Zoster (HZ), also called shingles. Reactivation of VZV occurs when cell-mediated immunity wanes due to aging or immunocompromising conditions, including autoimmune diseases or use of immunosuppressant medications [1,2].

The annual incidence of HZ among the general population is 3-7 cases per 1,000 person-years, increasing to 10 cases among persons older than 60 years, with an

estimated lifetime risk of 30% without vaccination [3,4]. It constitutes a healthcare burden because of its complications, including Postherpetic Neuralgia (PHN), the most common complication, occurring in up to 30% of the cases and is associated with increased mortality [4].

The incidence rates of hospitalization due to HZ infection in are up to 25 per 100,000 person-years [4,5]. The rates increase sharply with age, while a higher incidence was found in females [5,6]. In addition, PHN, bacterial infections, ocular and neurological involvement as well as disseminated HZ are documented as common indications for hospitalization. The reported average hospital stay is 5 days, with longer stays observed in patients with immunocompromising conditions and in older age groups [7,8].

The treatment outcome of HZ has been improved dramatically since the introduction of the anti-herpesvirus drugs in the 1980s. These agents, mainly Acyclovir, reduce pain, promote fast healing and prevent PHN [2].

In 2006, a live attenuated vaccine, Zostavax (ZVL), was the first anti HZ vaccine licensed. However, it is contraindicated in individuals with immunosuppressive conditions and in pregnancy [1,3]. A recombinant adjuvant VZV vaccine (RZV, Shingrix) was approved in 2017 and was updated in 2021 to include adults aged 18 years and older who are at increased risk of HZ due to immunodeficiency or immunosuppression therapy [3]. In Israel, ZVL had been included in the basic health services since 2012 for adults aged 60 years and older, while in 2023 Shingrix was introduced, with eligibility expanded to include immunosuppressed adults aged 18 years and older.

Our clinical impression is that the rate of hospitalizations due to HZ has increased in the recent years. The objectives of the study were to describe the demographic and the clinical characteristics of patients who were hospitalized with HZ over the years, the course of their disease and prognosis, as well as the impact of vaccination.

Methods

Study design

A retrospective cohort study which included adult patients (aged ≥ 18 years), who were hospitalized at one of Clalit Health Services' (CHS) seven hospitals (two tertiary centers) between 2002-2024 because of HZ infection (primary/main diagnosis). Patients with solid organ infection were excluded.

For each patient, the following data was extracted from the electronic medical records: demographic parameters (age and gender); comorbidities (according to previous diagnosis) (body mass index, smoking, ischemic heart disease, congestive heart failure, Chronic Obstructive Pulmonary Disease (COPD), diabetes mellitus, chronic renal and liver disease, Human Immunodeficiency Virus (HIV) infection, Rheumatoid Arthritis (RA), Systemic Lupus Erythematosus (SLE), Inflammatory Bowel Disease (IBD), active or history of malignancy (solid/ hematologic); organ transplantation [hematopoietic stem cell, kidney, lung, heart]; immunosuppressive treatment; the vaccination status; laboratory at admission (complete blood count, serum glucose, liver and kidney function tests), anti HZ treatment (medication, route and duration), in-hospital complications (PHN, ophthalmic involvement, meningitis, bacterial super infection, acute kidney injury, bone marrow suppression, gastrointestinal bleeding, pneumonitis and transfer to intensive care unit), length of hospitalization and both in-hospital and 30 days mortality.

The primary outcome was the number of patients who were hospitalized due to HZ per year. The secondary outcomes were the demographic and clinical parameters of the patients; the clinical course and outcome of the hospitalization. The tertiary outcomes were the demographic and clinical characteristics of the patients hospitalized in peripheral hospitals compared to the tertiary care ones; the prevalence of vaccination among the HZ hospitalized patients; as well as the characteristics associated with hospitalization for re-infection and mortality.

The study was approved by the local and CHS Helsinki Committees.

Statistical analysis

The statistical analysis was generated using SAS software, version 9.4 (SAS institute). Continuous data was expressed as mean ± standard deviation, median and interquartile range (25-75 percentile) as appropriate and was compared using T-test. Chi-square test was used for comparing dichotomous variables.

Results

Demographic and clinical characteristics

The study group included 3,921 patients, who were hospitalized due to HZ at CHS hospitals in Israel between January 2002 and December 2024. Fourteen subjects with a main diagnosis of HZ pneumonitis were excluded.

Figure 1 illustrated the numbers of hospitalizations for HZ per year. Over the study period, the hospitalization rates varied between initial rise, stabilization and subsequent reduction toward the end of the study period. In the early 2000s, the incidences were between 133 and 163 patients annually, followed by a gradual increase that culminated in 2018 (up to 237). Between 2019 and 2022, the yearly numbers stabilized at higher levels (180-215 patients), after which a steady decline was observed, with 193 patients in 2023 and 154 in 2024.

The demographic and clinical characteristics of the patients are presented in **Table 1**. The mean age was 68±18 years, equal rates between genders (52% females), the majority of hospitalizations (57%) were at the two tertiary care centers. Among the comorbidities, the most common ones were immunosuppressive therapy (49%), a diagnosis of

malignancy (43%) (solid 29% and hematologic 14%), diabetes mellitus (39%), ischemic heart disease (32%) and chronic kidney disease (27%), of whom fifth were on dialysis. Also, 327 patients (8%) were organ transplant recipients, including 234 (6%) with solid organ transplants and 95 (2%) who had undergone bone marrow transplantation; Notably, a subset of patients had received multiple organ transplants. Overall, only 19 patients (0.49%) were vaccinated against HZ.

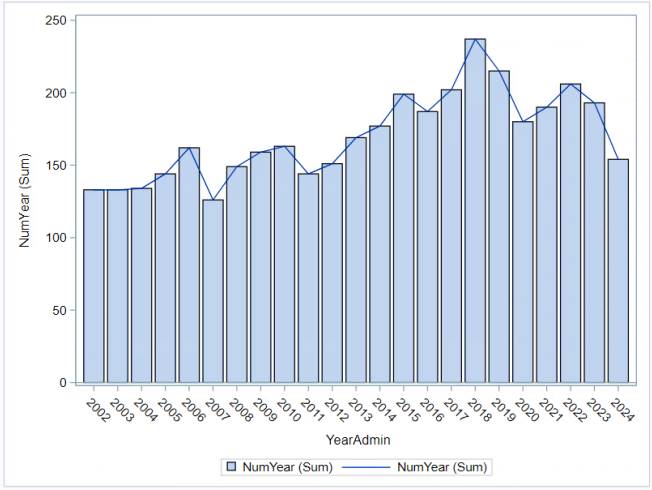

Figure 1: The numbers of hospitalizations for Herpes Zoster per year.

Table 1: Demographic and clinical characteristics of the study group (N=3907).

Age, year, mean (Std)	68	18.1
Gender, female no. (%)	2033	52
Hospitalization at tertiary care centers no. (%)	2210	56.6
Body mass index mg/kg² (n=1486), mean (Std)	27	5.5
Comorbidities	no.	(%)
Immunosuppressive therapy	1912	48.9
Malignancy	1667	42.7
Solid malignancy	1122	28.7
Hematological malignancy	545	13.9
Diabetes mellitus	1542	39.5
Ischemic heart disease	1253	32.1
Chronic kidney disease	1045	26.8
Smoking history	1022	26.2
Past smoker	599	15.3
Active smoker	423	10.8
Congestive heart failure	635	16.3
Chronic obstructive pulmonary disease	635	16.3
Liver disease	476	12.2
Post transplantation[1]	327	8.4
Solid organ transplantation	234	5.9
Hematopoietic stem cell transplantation	95	2.4
Inflammatory bowel disease	86	2.2
Rheumatoid arthritis	72	1.8
Systemic lupus erythematosus	70	1.8
Human immunodeficiency virus infection	30	0.8

[1]Several patients had multiple transplants-two recipients of bone marrow transplantation also underwent solid organ transplantation; among the solid organ transplant recipients, seven had received either an additional organ or a bone marrow transplant.

Clinical course and outcomes of hospitalization

Among the 1,916 patients with available data on antiviral treatment, 96% were treated with Acyclovir, the rest received Valacyclovir. The most common route of treatment was intravenous (50%). The mean duration of antiviral treatment was 6 ± 4 days. The mean duration of hospital stay was 7 ± 5 days.

Most of the patients (81%) did not receive any antibiotic treatment. Among those who were treated with antibiotics, Cephalosporins represented the most commonly used ones, accounting for 67%.

The most common complications were neurologic involvement, with PHN being the most frequent (266 patients (7%)). Bacterial superinfection was reported in 157 patients (4%) and ophthalmic involvement in 84 (2%). The most common systemic organ-related injury was acute kidney injury, observed in 65 patients (2%), bone marrow suppression in 16 patients (0.4%) and gastrointestinal bleeding in 7 (0.2%). Notably, 13 patients required admission to intensive care units, of whom 4 died (31%). The overall 30-days mortality was 2%.

Hospitalization in tertiary care hospitals compared to peripheral hospitals

Several statistically significant differences were observed between patients who were hospitalized at tertiary hospitals (N=2,210) and those admitted to peripheral ones (N=1,697) **(Table 2)**. The tertiary hospitals' patients received more frequently immunosuppressive therapy (52% *vs.* 44%, p<0.001), had higher rates of chronic kidney disease (28% *vs.* 24%, p=0.01) and a history of organ transplantation (12% *vs.* 4%, p=0.03). Antiviral therapy with Acyclovir was administered more frequently at tertiary hospitals (53% *vs.* 39%, p<0.001), typically *via* IV route (31% *vs.* 15%, p<0.001). However, antibiotic use for super-infection was higher in the peripheral hospitals (22% *vs.* 17%, p<0.001). Neurologic and ophthalmic complications were more frequent in peripheral hospitals (13% *vs.* 9%, p<0.001). The mortality rates did not differ significantly between the groups.

Table 2: The characteristics of patients hospitalized in a tertiary care hospital *vs.* peripheral hospitals.

	Tertiary hospitals (N=2210)	Peripheral hospitals (N=1697)	P-value
Age, year	66 (18.2)	70 (17.7)	<0.001
Gender, female	1137 (51.5)	896 (52.8)	0.4
Body mass index mg/kg[2]	27 (7.2)	27 (5.8)	1
Comorbidities			
Immunosuppressive therapy	1165 (52.7)	747 (44.0)	<0.001
Malignancy[1]	965 (43.7)	702 (41.4)	0.2
Diabetes mellitus	872 (39.5)	670 (39.5)	1
Ischemic heart disease	682 (30.9)	571 (33.7)	0.1
Chronic kidney disease	626 (28.3)	419 (24.7)	0.01
Smoking history[2]	598 (27.1)	424 (25.0)	0.5
Chronic obstructive pulmonary disease	357 (16.2)	278 (16.4)	0.9
Congestive heart failure	353(16.0)	282 (16.6)	0.6
Post Transplantation	265 (12.0)	62 (3.7)	0.03
Inflammatory bowel disease	48 (2.2)	38 (2.2)	0.9
Rheumatoid arthritis / SLE[3]	45 (2.0)/45 (2.0)	27 (1.6)/25 (1.5)	0.3/0.2
Human immunodeficiency virus infection	17 (0.8)	13 (0.8)	1
Antibiotics treatment during hospitalization	366 (16.6)	378 (22.3)	<0.001
In hospital complications			
Neurologic/ophthalmic complications[4]	197 (8.9)	213 (12.6)	<0.001
Bacterial super infection	63 (2.9)	94 (5.5)	<0.001
Length of hospitalization (days)	7 (4.9)	6 (4.8)	<0.001
In hospital mortality/30-days mortality	15 (0.7)/ 45 (2.0)	16 (0.9)/ 34 (2.0)	0.4/1

Note: All values are presented as n (%) or mean ± SD.
[1]Solid or hematologic malignancies
[2]Smoking history including past and active smoker
[3]SLE- Systemic lupus erythematosus
[4]Including post-herpetic neuralgia, ocular involvement and meningitis.

Hospitalization following re-infection

Re-hospitalization due to HZ re-infection occurred in 33 patients (0.84%), one of whom had even a third episode. Their mean age was 68 ± 16 years, 55% women. Seventeen patients (52%) were hospitalized at a tertiary care hospital. Most patients (73%) were receiving immunosuppressive therapy, 15 (45%) had a known malignancy and 12 (36%) patients were diabetic.

Characteristics of 30-day survivors and non-survivors

The in-hospital mortality rate was 0.8%, while 79 patients (2%) died within 30 days. The characteristics of patients who died within 30 days of hospitalization are presented in **Table 3**. Non-survivors were significantly older (mean age 80 ± 12 *vs.* 67 ± 18 years, p<0.001), had malignancy (67% *vs.* 42%, p<0.001), ischemic heart disease (57% *vs.* 32%, p<0.001), chronic kidney disease (48% *vs.* 26%, p<0.001) and congestive heart failure (34% *vs.* 16%, p<0.001). Intensive care unit treatment was significantly more common among patients who died (18% *vs.* 2%, p<0.001). The hospitalization was also longer in the non-survivor group (9 ± 6 *vs.* 7 ± 5 days, p<0.001).

Table 3: Differences in characteristics between 30-day survivors and non-survivors.

	Survivors (N=3828)	Non-survivors (N=79)	P-value
Age, year	67 (18.1)	80 (12.3)	<0.001
Gender, female	1993 (52.1)	40 (50.6)	0.001
Body mass index mg/kg[2]	27 (6.8)	24 (4.8)	0.006
Comorbidities			
Immunosuppressive therapy	1875 (49.0)	37 (46.8)	0.7
Malignancy[1]	1614 (42.2)	53 (67.1)	<0.001
Diabetes mellitus	1504 (39.3)	38 (48.1)	0.1
Ischemic heart disease	1208 (31.6)	45 (57.0)	<0.001
Chronic kidney disease	1007 (26.3)	38 (48.1)	<0.001
Smoking history[2]	1000 (26.1)	22 (27.9)	0.3
Chronic obstructive pulmonary disease	616 (16.1)	14 (17.7)	0.7
Congestive heart failure	608 (15.9)	27 (34.2)	<0.001
Post Transplantation	322 (8.4)	5 (6.3)	0.7
Inflammatory bowel disease	85 (2.2)	1 (1.3)	1
Rheumatoid arthritis /SLE[3]	70 (1.8)/ 69 (1.8)	2 (2.5)/1 (1.3)	0.7/1
HIV infection	29 (0.8)	1 (1.3)	0.5
Length of antiviral treatment (days)	5.73 (3.6)	5.95 (3.7)	0.8
In hospital complications			
Neurologic/ophthalmic complications[4]	407 (10.6)	3 (3.8)	0.1
Bacterial super infection	151 (3.9)	6 (7.6)	0.1
Supportive care indicators	69 (1.8)	14 (17.7)	<0.001
Length of hospitalization (days)	6.54 (4.9)	9.16 (5.6)	<0.001

Note: All values are presented as n (%) or mean ± SD
[1]Solid or hematologic malignancies
[2]Smoking history including past and active smoker
[3]SLE- Systemic lupus erythematosus
[4]Including post-herpetic neuralgia, ocular involvement and meningitis.

Discussion and Conclusion

The study results summarize the demographic and clinical characteristics of 3,907 patients who were hospitalized due to HZ at CHS hospitals in Israel between 2002 and 2024.

Although our primary impression, there was no significant increase in the rate of hospitalizations attributable to HZ over the study period. The rates increased modesty between 2002 to 2006 (from 2.0-2.3 per 100,000 persons), followed by a subsequent decline to 1.54 per 100,000 persons toward the end of the study period. A systematic review of 130 studies from 26 countries up to December 2013 reported that hospitalization rates for HZ varied widely, from 2 to 25 per 100,000 person-years, with higher rates observed in elderly populations [4]. In the United States, rates declined between 2001 and 2015 (from 8.6 to 6.8 per 100,000) [8] and in Italy, hospitalization rate was 10.4 per 100,000 persons-year with a significant decreasing trend from 13.9 in 2003-2006 to 7.8 in 2015-2018 [5]. In Poland a population-based study covering 2012-2021 found relatively stable hospitalization rates of 5.8 per 100,000 annually, whereas in Spain the incidence increased significantly from 10.81 to 16.97 per 100,000 person-year between 2003 and 2013, with an average annual rise of 2.8% [6,9].

Several studies reported an increase in HZ cases during the COVID-19 pandemic, possibly related to lymphopenia and impaired cell-mediated immunity [10]. In contrast, we observed a decrease in the incidence of hospitalizations for HZ in 2020 to 1.9 per 100,000, coinciding with the COVID-19 pandemic. It might reflect stricter hospitalization criteria and an overall reduction in hospital admissions for various conditions during the pandemia, rather than a true decline in disease burden. This is consistent with the report by Irigoyen-Mansilla et al. which showed that although hospitalization rates for respiratory infections increased during the pandemia, admissions for other infections pathologies decreased [11].

Immunosuppressive therapy was the most frequent comorbidity among our patients, affecting 49% of the study population. Malignancy, diabetes mellitus and ischemic heart disease were also common affecting 43%, 39% and 32% of hospitalized patients, respectively. Notably 8.4% of patients were organ transplant recipients, whereas autoimmune diseases such as RA and SLE were rare (1.8% each). These findings align with previous studies showing that specific comorbidities increase the risk of HZ, including: immunocompromised states, particularly hematopoietic stem cell transplantation and solid organ transplantation (OR=4.5). Other meaningful risk factor is malignancy, which is associated with a twofold increased odds of developing HZ [12]. Moreover, diabetes, kidney and pulmonary disease, as well as autoimmune conditions such as RA, SLE, IBD, psoriasis and HIV infection, were identified as risk factors for HZ [5,12-15]. Additionally, in our study, hospitalization for re-infection occurred in 0.84% of patients, predominantly in women and those with underlying comorbidities, reflecting the same risk factors reported in prior studies, where recurrence affected up to 5%-6% of cases [4].

HIV infection was identified in 30 (0.77%) of our patients. This finding conflicts with Grabar et al. findings which demonstrated that the incidence of HZ is approximately 3 times higher among patients with HIV infection compared to the general population, with an even greater excess risk up to 6-fold in the 15 to 44-year age group [16]. The main contributing factors to our low incidence are the relatively low rate of HIV infection in Israel, followed by the availability of anti-retroviral treatment [17].

Antiviral therapy is essential in managing HZ, as it reduces viral replication, lessens symptom severity and duration, as well as lowers the risk of PHN [1,2]. Recent studies report variability in antiviral therapy use for HZ; Baumrin et al. found that 77% of patients with severe HZ were treated by Acyclovir for a median duration of 14 days, typically, starting with 4 days of IV therapy before switching to oral [18]. The median length of hospitalization ranged from 8-10 days [5,18,19]. In our study, Acyclovir was the most commonly used antiviral agent (95%), with a median duration of treatment of 5 days (IQR 3-8). The median length of hospital stay was 6 days (IQR 4-8).

HZ prophylaxis is an important public health consideration. In our study, only 19 (0.45%) patients were documented as having been vaccinated, this can be attributed to limited awareness regarding the importance of the vaccine, as well as restricted indications within the Israeli health basket, where until January 2023, Zostavax was the exclusive vaccine available and was given to individuals aged 65 and older, with contraindication in immunocompromised individuals and during pregnancy. In January 2023, the Shingrix vaccine was introduced, indicated for individuals aged 50 or 65 and older (depending on the complementary health insurance), as well as for immunosuppressed patients aged 18 and above.

Importantly, a relative transient rise in HZ-related hospitalizations was observed following the introduction of the vaccine in Israel during 2012. Several studies have examined the impact of varicella vaccination on HZ incidence; According the exogenous boosting hypothesis, natural exposure to VZV may enhance VZV-specific cell-mediated immunity and thereby suppress viral reactivation; thus, widespread vaccination reducing wild-type virus circulation leading to a decrease in the opportunity for boosting immunity against VZV and a transient rise in the incidence of HZ in the population [20]. We also suggest that the observed transient increase in

hospitalization incidence after vaccine introduction may, in part, reflect heightened clinical awareness and improvements in case reporting.

Although PHN is typically the most common HZ complication, affecting up to 30% of patients, with ophthalmic and neurological complications reported in 12-19% and 10%-23% of hospitalized cases respectively, our study found a lower complication burden: PHN occurred in 7% of patients, secondary bacterial infections in 4% and ophthalmic or neurological complications in only 2% [4,5,13,19].

Although mortality from HZ is extremely low, estimated from 0.017 to 0.465 per 100,000 person-years in studies, a large Japanese study reported an in-hospital mortality rate of 1% [4,14]. In our study, the overall 30-day mortality rate, including both in-hospital and post-discharge deaths, was 2%, of which 39% occurred during hospitalization. Patients who died within 30 days were older and had a higher prevalence of immunosuppressive therapy and malignancy, as well as cardiopulmonary comorbidities.

Regarding the comparison of hospitalization settings, direct comparative data between tertiary and peripheral hospitals are limited; However, tertiary centers generally admit older, immunocompromised patients with more comorbidities often requiring intensive treatment [15]. Despite these differences, in our study, lengths of hospitalization and mortality rates were similar, indicating comparable overall outcomes across hospital settings.

The study has several limitations inherent to its retrospective design. Data accuracy relied on the quality and completeness of medical records, which may have led to misclassification or missing variables. Additionally, there is a possibility of underreporting adverse events due to dependence on passive documentation, potentially resulting in an incomplete assessment of safety outcomes.

In conclusion, our study supports previous findings describing the demographic, clinical characteristics as well as the illness course and associated prognosis of patients hospitalized due to HZ. Taken together, the findings reinforce the current recommendations that adult and immunocompromised patients should be vaccinated against HZ.

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Conflict of Interest

There was no conflict of interest.

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