

# Clinical and epidemiological aspects of herpes zoster disease in a primary care setting in Riyadh, Saudi Arabia: A retrospective cohort study

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## ABSTRACT

**Context:** Herpes zoster (HZ), or shingles, is one of the most common infectious diseases. HZ can be associated with other diseases, such as cancer and immunocompromised conditions. Thus, early recognition of the disease characteristics and clinical manifestations is critical to decrease the disease burden and to avoid further complications. **Aim:** To assess the epidemiology of HZ disease, its clinical manifestations, coexisting and post-existing conditions, complications, and management among patients in a primary care setting. **Subjects and Methods:** This was a retrospective, single-armed, cohort study. Data of all patients diagnosed with HZ, aged 18 years and older, who visited the Family Medicine Department at King Faisal Specialist Hospital and Research Center from January 2014 to August 2021 were reviewed from their medical records. All data analyses were performed using IBM Statistical Package for the Social Sciences (SPSS) statistical software, version 20.0. **Results:** A total of 330 cases were included over the study period. The male-to-female ratio was 1:2, with a higher occurrence of HZ (44.5%) in those aged  $\geq 50$  years. Only 4.5% of the patients were recipients of zoster vaccines. Thoracic dermatome was the most affected dermatome (38%). The most common coexisting disease was diabetes (21.5%). The most common post-existing disease was cardiovascular disease (3%), and the most common complication was postherpetic neuralgia (15.2%). Suboptimal dosage of acyclovir was the most commonly used treatment for HZ infections (69.7%). **Conclusions:** Zoster vaccination uptake was low. A national program for adult vaccination, including zoster vaccination, should be developed, and a guideline to direct primary health-care professionals in the management of HZ infections should be implemented.

**Keywords:** Clinical Manifestation, cohort study, epidemiology, herpes zoster, Saudi Arabia, shingles

## Introduction

Herpes zoster (HZ), also known as shingles, occurs as a result of the reactivated varicella zoster virus that is latent in a sensory ganglion during the primary infection (varicella).<sup>[1]</sup> It is characterized by

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a painful, blistering dermatomal rash.<sup>[2]</sup> Nevertheless, some patients have reported prodromal pain, which often confuses the diagnosis until a skin eruption appears.<sup>[3]</sup> The incidence and severity of HZ disease have been reported to increase with age, markedly after 50 years of age. This can be attributed to an aging-related decline in the immunity of elderly people. However, although rare, children can also be infected by HZ. Half of the adults who reached 85 years of age were estimated to have suffered from HZ at least once in their lives.<sup>[4]</sup> Based on

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prospective surveillance and medical record data, studies in North America, Europe, and Asia-Pacific have shown that the incidence of HZ disease was three to five per 1000 person-years over all, six to eight per 1000 person-years at the age of 60, and eight to 12 per 1000 person-years at the age of 80.<sup>[2]</sup> The incidence of HZ is determined by factors affecting the host immune system, such as advanced age, autoimmune diseases, cellular immune dysfunction, and those who received chemotherapy or steroids. In fact, these patients have a 20–100 times greater risk for HZ than immunocompetent individuals.<sup>[3]</sup> Furthermore, HZ is associated with an increased risk of certain cancers such as non-melanoma skin cancer.<sup>[5]</sup> Many complications have been reported as a result of HZ infection. For example, postherpetic neuralgia is considered one of the most common HZ complications.<sup>[3]</sup> Although some studies have proposed that varicella vaccine aggravates the burden of zoster, a US population-based cohort study conducted over 60 years showed the unlikelihood of this scenario.<sup>[6–8]</sup> A new zoster vaccine (Shnigrix) showed a high efficacy of 97.2% across all elderly age groups.<sup>[9]</sup> Although HZ disease causes a substantial economic burden, the HZ vaccine was found to be a cost-effective measure.<sup>[10]</sup> Many studies have described the characteristics of HZ disease, its manifestation, and complications worldwide, but no study has yet evaluated HZ in a community setting in Saudi Arabia. In this study, we assess the epidemiology of HZ disease, its clinical manifestation, coexisting and post-existing conditions, complications, and management in a primary care setting in Saudi Arabia.

## Subjects and Methods

A retrospective cohort study was conducted in which data of all patients diagnosed with HZ, aged 18 years and older, who visited the Family Medicine Department at King Faisal Specialist Hospital and Research Center (KFSH&RC) from January 2014 to August 2021 were reviewed from their medical records after obtaining the necessary ethical approval from KFSH&RC (reference No. 2211183). Demographic data, clinical manifestations of HZ, and coexisting (defined as diseases that occurred before the diagnosis of HZ disease) and post-existing (defined as diseases that occurred after the diagnosis of HZ disease) conditions within 2 years from the time of diagnosis, including diabetes mellitus, cardiovascular diseases, chronic liver disease, immunocompromised conditions (due to transplant, underlining malignancy, or immunosuppressant drugs), and renal failure, were collected. Complications, laboratory results, patients' previous medical history, and treatment received were also retrieved or noted.

## Statistical analysis

All data analyses were performed using IBM Statistical Package for the Social Sciences (SPSS) statistical software, version 20.0. Descriptive statistics were conducted to explain the demographic information, clinical manifestation, coexisting diseases, post-existing diseases, complications of HZ, and its management. The population size served by KFSH&RC is approximately 50,000. The size of each age group was approximated to the

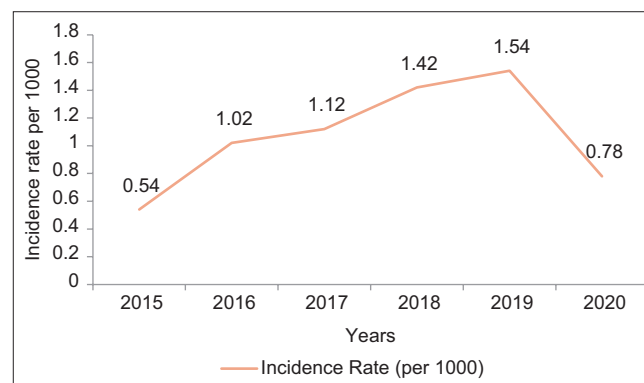
population of Saudi Arabia according to governmental statistics. The incidence of HZ was calculated in each age group in proportion to the total number of our study sample size. Age was converted to dichotomous categories (<50, ≥50) based on a high-risk age group. All data were summarized into tables showing the frequencies and percentages in each category. Bivariate analysis was conducted to measure the association of different risk factors, including personal characteristics, varicella vaccination, and HZ vaccination, with the development of HZ disease. The hypothesis was tested at a 0.05 significance level.

## Results

A total of 330 cases of HZ were identified in the Family Medicine Department at KFSH&RC from January 2014 to August 2021. The mean incidence rate of HZ disease was 1.4/1000 population, with a temporal increase from 1.1/1000 population in 2017 to 1.5/1000 population in 2019 and a decline in reported cases in 2020 [Figure 1]. Of the 330 collected cases, 67% (221/330) were female. The mean age of patients at the time of diagnosis was 47.17 years, with 44.5% and 22.1% of patients aged ≥50 and ≥60 years, respectively. The incidence rate generally increased with age, with the incidence being the highest among the elderly at 3/1000 and 3.8/1000 population in those aged ≥50 and ≥60 years, respectively [Table 1]. Saudis comprised 67.9% of the total cases, and the rest were expatriates. Of the 330 patients, only 4.8% and 4.5% were vaccinated by varicella and zoster vaccines, respectively. Among those ≥50 years of age, only 10.2% received the zoster vaccine. Among the patients, 87.9% were diagnosed correctly at the first presentation.

Unilateral pain (96.4%) was the most manifested clinical characteristic after rash; only 1.5% of patients reported bilateral pain. Conversely, 7.3% did not report any pain. Itchiness was reported in 76.8% of cases. In our study, pain appeared before the rash in 68% of patients.

Among the different dermatomes, thoracic dermatomes (38%) were the most common, followed by maxillary–mandibular dermatomes (29.8%) and lumbosacral dermatomes (13.9%) [Table 2]. Our study showed a significance



**Figure 1:** Incidence of herpes zoster in Saudi Arabia, 2015–2020

in age difference with regard to dermatome involvement. Patients aged <50 years appeared to present with more maxillary–mandibular dermatomes (43.2%) compared to patients aged ≥50 years (11.9%) ( $P < 0.001$ ). Patients aged ≥50 years presented with more ophthalmic dermatome (9.1%) compared to patients aged < 50 years (3.3%) ( $P < 0.05$ ).

In this study, 30.1% of patients had coexisting diseases. The most common coexisting disease was diabetes (21.5%), followed by immunocompromised conditions (19.4%) [Table 3]. Patients who developed post-existing diseases mostly had cardiovascular diseases (3%) [Table 4]. Among the 20.9% that developed complications, postherpetic neuralgia (PHN) was the most common (15.2%). In fact, elderly patients aged ≥50 years (24.5%) and immunocompromised patients (34%) were significantly associated with PHN ( $P < 0.01$ ). Other complications were less frequent [Table 5]. As per management, a suboptimal dosage of acyclovir (69.7%) was the most common antiviral drug used;

paracetamol/nonsteroidal anti-inflammatory drugs (NSAIDs) was used in 79.5% of cases [Table 6].

## Discussion

### Epidemiology of HZ

An increasing trend of HZ cases was found in 2017–2019 and a decline in reported cases in 2020, possibly due to the coronavirus disease 2019 (COVID-19) pandemic. This pattern of HZ occurrence incorporates the worldwide increase in HZ cases over the years.<sup>[6,11,12]</sup> Despite being a minority among the Saudi population, the elderly constituted a major proportion (44.5%) of HZ patients. The equivalence in HZ occurrence between the young age group (30–39 years) and the elderly age group (50–59 years) could be attributed to the fact that the young population constitutes the majority of the country's population. This study showed that HZ is predominant among females, with a male-to-female ratio of 1:2. On the contrary, previous local and regional studies have reported the male-to-female ratios as 2:1, 4:1, and 1.5:1 in Saudi Arabia, Qatar, and Iran, respectively.<sup>[3,11,13]</sup> This variation between the current study and the local study in terms of gender predominance could be attributed to the fact that this study was community based, targeting primary care rather than a secondary level of care, thus offering a better representation of the disease epidemiology in Saudi Arabia. Moreover, Kawai and Yawn concluded that female predominance could be due to their health-care-seeking behavior and their hormonal and immunological makeup, which put them at a higher risk of getting HZ (relative risk = 1.31).<sup>[14]</sup> Two studies conducted in the USA and Brazil reported a higher risk of HZ among females, as the male-to-female ratio was approximately 1:2.<sup>[12,15]</sup> As our sample was composed of Saudis (67.6%), the nationality distribution in the study sample mimicked the population distribution in the country. A low percentage of the study sample was vaccinated, which could be attributed to the low rates of vaccination with the zoster vaccine among the adult population in Saudi Arabia. Saudi Arabia has licensed the new zoster vaccine (Shingrix), but no national program has yet been implemented. Therefore, a national vaccination program is deemed necessary to control the burden of the disease. Based on an Australian study, the zoster vaccination coverage after 2 years of national implementation was estimated to be 47% comparable to that of other developed countries.<sup>[16]</sup> Therefore, the active role of primary health-care providers in raising the awareness of the community, accompanied by public access to the zoster vaccine, will lead to a higher and congruent vaccine uptake among the elderly population. In our study, 12.1% of patients were initially misdiagnosed, most likely due to the nonspecific initial presentation of HZ disease.

### Clinical manifestations of HZ

The majority of patients in HZ studies reported unilateral pain. Our study is not an exception, as 96.4% of our study population presented with unilateral pain, distributed dermatome-wise as a classical symptom of HZ. In terms of pain characteristics, 50.9% of

**Table 1: Distribution of herpes zoster cases and incidence rate as per the age group**

Age groups	n (%)	Incidence (per 1000)
18-29	56 (17)	0.93
30-39	74 (22.4)	1.03
40-49	53 (16.1)	0.89
50-59	74 (22.4)	2.49
60-69	39 (11.8)	3.14
>70	34 (10.3)	5.00
All	330 (100)	0.94

**Table 2: Dermatome distribution of herpes zoster cases**

Dermatome	Percentage
Thoracic	38
Maxillary + mandibular	29.8
Lumbosacral	13.9
Ophthalmic	8.6
Cervical	6.5
Maxillary	1.9
Mandibular	1.3

**Table 3: Coexisting diseases of herpes zoster cases**

Coexisting diseases	Percentage
Diabetes	21.5
Immunocompromised:	19.4
Transplant	3.3
Lymphoma/leukemia	3.3
SLE	2.4
AIDS	0.6
Chemotherapy	6.4
Radiation	2.7
Biological	4.8
Systemic steroids	11.5
Renal disease	7.9
Cancer	7.3
Chronic liver disease	3.4

AIDS=acquired immunodeficiency syndrome, SLE=systemic lupus erythematosus

**Table 4: Post-existing diseases of herpes zoster cases**

Post-existing diseases	Percentage within 2 years
Cardiovascular diseases:	3
Myocardial infarction	2.1
Transient ischemic attack	0.6
Stroke	0.3
Cancer	1.8
Renal disease	1.2
Diabetes	0.9
Chronic liver disease	0.6
Transplant	0.3

**Table 5: Complications of herpes zoster infections**

Complications	Percentage (frequency)
Postherpetic neuralgia	15.4
Ocular complications	2.2
Bacterial superinfection	0.9
Ramsay Hunt syndrome	0.6
Scarring	0.3

**Table 6: Management of herpes zoster cases**

Management	Percentage
Acyclovir	69.7
Famciclovir	41.7
Valacyclovir	2.2
Paracetamol/NSAIDs	79.5
Systemic steroids	9
Narcotics	7.4

NSAIDs=nonsteroidal anti-inflammatory drugs

patients reported continuous pain and 41.1% reported intermittent pain, similar to the findings of a French study in which 55% and 45% of patients reported continuous and intermittent pain, respectively.<sup>[17]</sup> Furthermore, a burning type of pain was reported in 62.6%, compared to 59.80% in the French study.<sup>[17]</sup> This shows a high similarity in the pain characteristics of HZ among different nations and a high prevalence of burning pain against the other types of pain.

Thoracic dermatome was the most affected dermatome in this study (38%), compared to 51%, 41.14%, and 61% in Saudi Arabia, Iraq, and France, respectively, where thoracic dermatome was also reported as the most common dermatome involved.<sup>[3,17,18]</sup> This finding is consistent with the majority of HZ studies in the literature showing that the thoracic dermatome is the most commonly affected dermatome in HZ around the world. Lumbosacral dermatomes accounted for 13.9% in our study, compared to 13.5%, 26.85%, and 22% in Saudi Arabia, Iraq, and France, respectively.<sup>[3,17,18]</sup> Although lumbosacral dermatomes are frequently involved, thoracic and trigeminal dermatomes are the most commonly affected dermatomes in most countries.

In terms of symptom chronology, pain precedes rash in some patients, which presents a challenge for physicians in diagnosing HZ patients early. In our study, pain preceded the rash in 68% of patients, compared with 74% of patients in France.<sup>[17]</sup>

## Coexisting diseases with HZ

Patients with diabetes and immunocompromised patients had the highest risk of developing HZ disease. Other studies have shown that decreased cell-mediated immunity is a contributing factor to HZ reactivation, including immunosuppressive disorders and therapies.<sup>[19]</sup> These risk factors were supported in the findings, as the most common coexisting diseases were diabetes (21.5%) and immunocompromised conditions (19.4%). A Japanese study showed that 35.5% of HZ cases were patients with diabetes.<sup>[19]</sup> Moreover, renal disease ranked as the third most common coexisting disease (7.9%). This is not uncommon, as 9.5% of renal disease patients were found to have HZ reactivation in a cohort study in Japan.<sup>[19]</sup>

## Post-existing diseases with HZ

The association between HZ disease and the risk of cardiovascular diseases, namely, myocardial infarction (MI) and stroke, remains unclear. This can be attributed to confounding factors that have not been adequately controlled in previous studies. Nevertheless, a comprehensive review showed that individuals who were infected by HZ or HZ ophthalmicus had a 1.3–4-fold increased risk for developing cardiovascular disease, with risk being the highest within the first year after an HZ episode and diminishing gradually after that.<sup>[20]</sup> According to a retrospective cohort study performed in the UK, a significant increased risk was found for transient ischemic attack and MI, regardless of age, and a higher risk of stroke was seen only in patients below 40 years of age.<sup>[21]</sup> This was also seen in our study, as 3% of patients developed cardiovascular diseases, mostly in the form of MI (2.1%), within 2 years of HZ diagnosis. The literature shows conflicting findings about cancer being a post-existing disease among HZ patients. A case–control study on US adults aged  $\geq 65$  years showed a significant association between HZ and oral, pharyngeal, lung, colon, non-melanoma skin, and diffuse large B-cell lymphoma cancers, among others.<sup>[5]</sup> However, in the current study, only six patients developed cancer within 2 years of HZ diagnosis. This low number of patients may be attributed to the fact that the HZ patients in this study were younger than those in the US case–control study, as the elderly population is generally at a higher risk for developing cancers due to the age factor, regardless of HZ disease.<sup>[5]</sup>

## Complications of HZ

The most common complication of HZ disease was PHN. PHN was reported in 15.2% of cases, in which the majority of patients (70%) were aged  $\geq 50$  years ( $P < 0.01$ ). This is consistent with a US study in which 20% of HZ patients experienced PHN, with 80% of them being aged  $\geq 50$  years.<sup>[22]</sup> The majority of PHN patients were immunocompromised ( $P < 0.01$ ).

## Management of HZ

Antiviral drugs have been shown to decrease the duration of the rash and the severity of the pain associated with the rash.<sup>[23]</sup> However, these benefits have been demonstrated only in patients who received antiviral medications within 72 h after the rash eruption.<sup>[24,25]</sup> Famciclovir has a pharmacological and clinical privilege, as it is taken at 500 mg orally three times a

day for 7 days, compared to acyclovir, which is taken at 800 mg five times a day for 7–10 days.<sup>[24,25]</sup> In addition, famciclovir has better bioavailability than acyclovir.<sup>[24]</sup> Conversely, in our study, acyclovir was prescribed more frequently, even when out of its window and at lower doses, deviating from the recommended guidelines. As a result, increasing physicians' awareness about proper antiviral medication and dosing is important.

## Conclusion

The strengths of this study are the use of a retrospective cohort and the study being conducted at the primary care level. Nevertheless, it also has some limitations, such as the potential lack of documentation from electronic medical records. Further nationwide studies are needed to provide a better understanding of the HZ burden on the economy and the health-care system in Saudi Arabia and Middle East and North Africa (MENA) region. This study highlights the low uptake of zoster vaccination and the importance of raising the awareness of the public and health-care professionals about HZ vaccination and its benefits. The management of HZ infection is suboptimal. A national program for adult vaccination, including zoster vaccination, should be developed, and a guideline to direct primary health-care professionals in the management of HZ infections and its potential complications should be established and endorsed.

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## Conflicts of interest

There are no conflicts of interest.

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