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# Risk Factors and Complications in Herpes Zoster Patients at Dr. Soetomo General Academic Hospital, Surabaya

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## ABSTRACT

**Introduction:** Herpes zoster (HZ) is a painful rash confined to a dermatome resulting from the reactivation of the varicella-zoster virus (VZV). Factors that increase the risk of HZ include age, sex, prior varicella infection, immunocompromised conditions, SARS-CoV-2 infection, and varicella vaccination. Potential complications of Herpes zoster may encompass post-herpetic neuralgia (PHN), Ramsay Hunt syndrome, meningoencephalitis, vasculopathy, and varicella pneumonia. This study aimed to identify risk factors and complications associated with Herpes zoster and to enhance preventive measures to decrease the incidence of Herpes zoster at Dr. Soetomo General Academic Hospital, Surabaya, Indonesia.

**Methods:** This descriptive, retrospective analysis utilized secondary data from the medical records of Herpes zoster patients at the Dermatology Clinic of Dr. Soetomo General Academic Hospital, Surabaya, Indonesia, from 2019 to 2021. Data analysis used the International Business Machines Corporation (IBM) Statistical Package for the Social Sciences (SPSS) version 25.0.

**Results:** Out of 105 cases, Herpes zoster was more frequently observed in females (61 patients, 58.1%), with the highest occurrence found in the 46–55 years old age group (33 patients, 31.04%). The thoracic nerve was the most frequently involved (58 patients, 55.2%). Hypertension emerged as the most prevalent risk factor (26 patients, 24.7%), followed by diabetes mellitus/DM (15 patients, 14.3%) and autoimmune disorders (7 patients, 6.7%). Most patients had no comorbidities (33 patients, 31.4%). Post-herpetic neuralgia was the most frequent complication (19 patients, 18.1%), while 78 patients (74.3%) reported no complications.

**Conclusion:** Herpes zoster was more prevalent among females, with hypertension being the most significant risk factor and post-herpetic neuralgia the most common complication.

**Highlights:**

1. The highest distribution of herpes zoster patients' age and gender was between 46-55 years old and females.
2. The highest distribution of herpes zoster patients' complications was post-herpetic neuralgia.

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## Introduction

Herpes zoster (HZ) is a distressing rash confined to a dermatome triggered by the reactivation of dormant varicella-zoster virus (VZV), which persists within the patient's sensory nerve clusters following a prior case of chickenpox. The progression of this condition can be segmented into four distinct stages: prodromal, acute, subacute, and chronic. The prodromal phase manifests 1-5 days before the emergence of the HZ rash. The acute phase of Herpes zoster typically persists up to 30 days post-rash onset. In individuals who later develop a chronic condition, an intermediate subacute phase occurs 30 to 90 days after the rash first appears.[1]

More than 95% of people above 50 years old worldwide have encountered VZV previously, rendering a significant portion of the world's population vulnerable to contracting HZ.[2] In the absence of immunization, individuals over 85 years old have an estimated 50% probability of developing HZ at some point.[2] This underscores the significance of prioritizing HZ prevention as a crucial global health concern.[2] A study consistently showed a notable rise in the incidence of zoster as individuals age, particularly after reaching 50 years old.[2] The average age of onset of zoster in adults (those aged 22 years old and above) is 59.4 years old, with 68% of cases occurring in those aged 50 years old and up.[2] Herpes zoster becomes more common as people age, but it rarely affects children.[3] Herpes zoster affects 1.5-3.0 people per 1,000 people every year, affecting people of all ages.[3] Data from 13 teaching hospitals in Indonesia showed 2,232 HZ patients between 2011 and 2013.[3] Peak cases of Herpes zoster occur at the age of 45-64 years old, as much as 37.95%, and females tend to have a higher incidence.[3]

During the initial infection, the virus enters a dormant state within several sensory ganglia, remaining latent for life. Herpes zoster arises as a secondary infection when the virus reactivates, typically spreading to a single dermatome. Acute HZ is generally marked by a vesicular rash on the skin within the affected dermatome, often accompanied by sharp pain. Before the appearance of the rash, patients may experience non-specific symptoms such as itching, burning sensations, or general symptoms (fever or malaise) in a phase known as the prodrome.[1] The incidence of HZ can be increased by risk factors, such as age, gender, experience of varicella before, immunocompromised, SARS-COV-2 virus, and COVID-19 vaccination (especially in elderly patients). Risk factors and comorbidities reduce cell-mediated immunity, elevating the susceptibility to viral infections, including zoster.[4]

Herpes zoster displays various stages with differing complications, notably post-herpetic neuralgia (PHN) and HZ vasculitis linked to severe outcomes. Renal and gastrointestinal issues are also noted.[5] A study revealed significantly reduced quality of life in patients with acute HZ, stressing the need for prevention and improved treatment to mitigate its impact on patients' well-being.[6] Therefore, it is necessary to conduct research on the risk factors and complications in HZ patients at the Dermatology Clinic of Dr. Soetomo General Academic Hospital, Surabaya, Indonesia, to determine risk factors and complications in HZ patients and assist in improving the prevention to reduce the prevalence of HZ patients at Dr. Soetomo General Academic Hospital, Surabaya, Indonesia.[3]

## Methods

This descriptive study drew data from the central medical records at Dr. Soetomo General Academic Hospital, Surabaya, Indonesia. Employing a total sampling method, it encompassed all eligible medical records meeting inclusion and exclusion criteria. Inclusion criteria involved patients at the Dermatology Clinic suffering from HZ within 2019-2020, detailing factors like age, gender, risk factors, and complications. Excluded criteria were incomplete medical records. The study utilized stationery, data sheets, and the International Business Machines Corporation (IBM) Statistical Package for the Social Sciences (SPSS) version 25.0 for data collection and analysis.[7] All statistical evaluations were conducted using IBM SPSS version 25.0, and the results were ultimately displayed through tables and charts.[7]

## Results

Herpes zoster mainly affected individuals aged 46 to 55 years old (31.4%), followed by those aged 56 to 65 years old (21.9%) and over 65 years old (13.3%) at Dr. Soetomo General Academic Hospital, Surabaya, Indonesia, between 2019 and 2021. Conversely, HZ rarely occurred in younger age groups: 0-5 years old (0.9%) and 5-11 years old (1.9%). Among younger patients, one aged 5-11 years old had autoimmune (systemic lupus erythematosus/SLE) as a risk factor. Additionally, the gender distribution over this period indicated a higher prevalence among females (58.1%) than males (41.9%) among the 105 patients studied.

Table 1. Distribution of age and gender

| Characteristics | n = 105 | Percentage (%) |
|---|---|---|
| **Age Groups (years old)** | | |
| 0-5 | 1 | 0.9 |
| 5-11 | 2 | 1.9 |
| 12-16 | 4 | 3.8 |
| 17-25 | 11 | 10.5 |
| 26-35 | 10 | 9.5 |
| 36-45 | 7 | 6.7 |
| 46-55 | 33 | 31.4 |
| 56-65 | 23 | 21.9 |
| ≥ 65 | 14 | 13.3 |
| **Gender** | | |
| Male | 44 | 41.9 |
| Female | 61 | 58.1 |

Source: Research data, processed

Table 2 shows that 15 (14.3%) Herpes zoster patients experienced varicella before they developed HZ. Of 88 patients (83.8%), some stated that they never had varicella before HZ. Two patients (1.9%) did not remember whether they had varicella before developing HZ. Some data on patients who did not remember exposure to varicella before developing HZ indicated several possibilities. Some

patients forgot whether they were exposed to varicella, while others might have been exposed but did not realize it was varicella.

Table 2. Experienced with varicella before

| Experienced Varicella Before | Gender | | Amount (n) | Percentage (%) |
|---|---|---|---|---|
| | Male | Female | | |
| Yes | 8 | 7 | 15 | 14.3 |
| Never | 35 | 53 | 88 | 83.8 |
| Not remember | 1 | 1 | 2 | 1.9 |
| Total | 44 | 61 | 105 | 100 |

Source: Research data, processed

The distribution of patients with comorbidities at the Dermatology Clinic of Dr. Soetomo General Academic Hospital, Surabaya, Indonesia, between 2019 and 2021 is as follows: the highest data was found in patients without comorbidities in a total of 33 patients (31.4%). Following that, the most common comorbid was hypertension, with a total of 26 patients (24.7%) consisting of 11 male patients and 15 female patients. Furthermore, there were 15 individuals (14.3%) with diabetes mellitus (DM) and SLE, with a total of 7 patients (6.7%). In addition, female patients were more likely to have comorbidities than male patients.

Table 3. Distribution of comorbidities

| Comorbidities | Gender | | Amount (n) | Percentage (%) |
|---|---|---|---|---|
| | Male | Female | | |
| Without comorbidities | 5 | 28 | 33 | 31.4 |
| Hypertension | 11 | 15 | 26 | 24.7 |
| Diabetes mellitus | 5 | 10 | 15 | 14.3 |
| Systemic lupus erythematosus | 1 | 6 | 7 | 6.7 |
| Sjogren's syndrome | 0 | 1 | 1 | 0.9 |
| Breast cancer | 0 | 4 | 4 | 3.8 |
| Lung cancer | 1 | 1 | 2 | 1.9 |
| Nasopharyngeal cancer | 1 | 0 | 1 | 0.9 |
| Renal cell carcinoma | 1 | 0 | 1 | 0.9 |
| Asthma | 1 | 2 | 3 | 2.9 |
| Hemodialysis | 2 | 1 | 3 | 2.9 |
| Drug hypersensitivity | 0 | 3 | 3 | 2.9 |
| Cholesterol | 1 | 0 | 1 | 0.9 |
| Chronic kidney disease | 1 | 0 | 1 | 0.9 |
| Human immunodeficiency virus | 0 | 1 | 1 | 0.9 |
| Pregnancy | 0 | 1 | 1 | 0.9 |
| SARS-CoV-2 virus | 1 | 0 | 1 | 0.9 |
| Tuberculosis | 1 | 0 | 1 | 0.9 |
| Tuberculous spondylitis | 1 | 0 | 1 | 0.9 |
| Total | 33 | 73 | 106 | |

*One subject might have more than one comorbidity
Source: Research data, processed

The distribution of patients with hypertension and other comorbidities between 2019 and 2021 at the Dermatology Clinic of Dr. Soetomo General Academic Hospital, Surabaya, Indonesia, is as follows: the highest data was discovered in patients with hypertension and DM, with a total of 11 patients (42.3%). In addition, there were 4 patients (15.4%) with hypertension who did not also have any other comorbid conditions. Furthermore, 3 patients (11.5%) also had cancer and hemodialysis treatment as additional comorbidities.

Table 4. Distribution of hypertension

| HT*Other Comorbidities | Amount (n) | Percentage (%) |
|---|---|---|
| HT*Diabetes mellitus | 11 | 42.3 |
| HT*Hemodialysis | 3 | 11.5 |
| HT*Cancer | 3 | 11.5 |
| HT*Chronic kidney disease | 1 | 3.8 |
| HT* Human immunodeficiency virus | 1 | 3.8 |
| HT*Asthma | 1 | 3.8 |
| HT*Tuberculous | 1 | 3.8 |
| HT* Systemic lupus erythematosus | 1 | 3.8 |
| HT*Without other comorbidities | 4 | 15.4 |
| Total | 26 | 100 |

*One subject might have more than one comorbidity
Source: Research data, processed

The distribution of Herpes zoster disease at the Dermatology clinic of Dr. Soetomo General Academic Hospital, Surabaya, Indonesia, from 2019 to 2021 is as follows: the highest data was found in patients without complications in a total of 78 patients (74.3%). Following that, the most common complication was PHN, which affected 19 patients (18.1%). Furthermore, there were 7 patients (6.7%) who experienced complications of secondary bacterial infection. In addition, female patients were more likely to have complications than male patients.

Table 5. Distribution of hypertension

| Complication | Gender | | Amount (n) | Percentage (%) |
|---|---|---|---|---|
| | Male | Female | | |
| No complications | 28 | 50 | 78 | 74.3 |
| Post-herpetic neuralgia | 12 | 7 | 19 | 18.1 |
| Secondary bacterial infection | 3 | 4 | 7 | 6.7 |
| Ramsay Hunt syndrome | 1 | 0 | 1 | 0.9 |
| Meningoencephalitis | 0 | 0 | 0 | 0 |
| Vasculopathy | 0 | 0 | 0 | 0 |
| Varicella pneumonia | 0 | 0 | 0 | 0 |
| Total | 44 | 61 | 105 | 100 |

Source: Research data, processed

## Discussion

Herpes zoster patients at the Dermatology Clinic of Dr. Soetomo General Academic Hospital, Surabaya, Indonesia, were dominated by the age range of 46-55 years old, with a total of 33 patients (31.4%), followed by the age range of 56-65 years old, with a total of 23 patients, or approximately 21.9%. One similar study showed that the age at the time of the initial diagnosis of zoster was 41.1 years old.[8] As time advances, individuals age and become more prone to zoster. Consequently, the relative risk of developing zoster is anticipated to rise 10-20 years post-exposure. This indicates that HZ disease becomes more frequent as people get older.[8] Similar to a previous study, this study emphasizes a greater incidence of HZ in children vaccinated after 5 years old compared to those vaccinated between 12 and 18 months old. Before vaccination, HZ incidence stood at 46 per 100,000 cases for children under

14 years old. The increase in Herpes zoster among healthy children might be linked to the initial varicella infection during pregnancy or infancy when immunity was not fully established.[9]

The highest prevalence of gender distribution in HZ patients at the Dermatology Clinic of Dr. Soetomo General Academic Hospital, Surabaya, Indonesia, was found in females, with females totaling 58.1% and males totaling 41.9% of 120 patients. A study stated that hormonal or biological differences between genders could contribute to this phenomenon.[10] The menopausal transition phase is linked to a heightened incidence of HZ in females, attributable to hormonal shifts affecting their immune response.[10] According to a recent study, females might have a different immune response to latent viral infection than males.[11]

The highest data was found at Dr. Soetomo General Academic Hospital, Surabaya, Indonesia, in HZ patients without complications (ICD B02.9), with as many as 69 patients (65.7%). In this study, 19 patients (18.1%) were diagnosed with PHN (ICD B02.22), which is in line with a study reported that the prevalence of PHN after exposure to HZ occurred in 835 patients with a prevalence of 2.3%, which occupied the highest place in the disease in HZ.[12] The most affected dermatomes included thoracic (53%), cervical (20%), and trigeminal (15%), with ophthalmic involvement. Transmission of the infection to non-immune individuals occurs at low rates through direct skin contact or inhaling infected droplets.[13] According to this study, the thoracic nerve affected 58 patients with HZ, 38 females and 20 males (55.2%). The cervical nerve HZ of 26 patients, consisting of 17 females and 9 males (24.7%), was then diagnosed, along with the cranial nerve HZ of 23 patients (21.9%).

This study found data on 33 patients without comorbidities, with 5 males and 28 females (31.4%). In this study, 26 patients had hypertension as a risk factor for HZ, with 11 males and 15 females (24.7%). A different investigation, a Japanese retrospective cohort study conducted in a hospital setting, corroborated this result by demonstrating that individuals with hypertension or DM exhibited markedly higher risks of HZ compared to those with other pre-existing conditions.[14] A recent analysis indicated that VZV infects cerebral blood vessels, resulting in inflammation and thickening of the intima, contributing to vascular blockage in VZV-associated vasculopathy.[15] HZ represents a notable risk factor for stroke within one year following the episode, although there are limited reports on antiviral treatment reducing this risk.[15] As shown in Table 5, hypertension frequently coexists with other comorbidities. Eleven patients with hypertension also had diabetes (42.3%), 3 patients with hypertension who also had hemodialysis and cancer (11.5%), and 1 patient with hypertension who also had chronic kidney disease (CKD), asthma, tuberculosis, and SLE (3.8%). Furthermore, only 4 patients (15.4%) had hypertension as a comorbidity. Hypertension and diabetes are widespread, interconnected ailments that exhibit significant overlap in their underlying risk factors, including ethnicity, familial background, dyslipidemia, and lifestyle factors. These conditions can lead to both microvascular and macrovascular complications. Notable macrovascular issues associated with long-term diabetes or hypertension encompass coronary artery disease, myocardial infarction, stroke, congestive heart failure, and peripheral vascular disease.[16]

This study revealed that DM appeared as a risk factor in 15 patients, involving 10 females and 5 males of HZ patients (14.3%). A recent study noted that individuals with DM have weakened immunity, making them more prone to infections.[5] Specifically, impaired cell-mediated immunity, phagocytosis, and opsonization increase susceptibility. Multiple studies highlight DM as a significant risk factor for HZ and PHN, potentially worsening the severity of the condition's clinical course.[5] In this study, there were cases of autoimmune disease, including 7 patients with SLE, 6 females and 1 male (6.7%), and 1 patient with Sjogren's syndrome (0.9%). A previous study discovered that in immunocompromised individuals, HZ infection can disseminate and pose a life-threatening risk.[17] SLE patients are particularly susceptible to HZ reactivation due to the intrinsic immune aberrations of the disease and immunosuppressive therapies. Recent meta-analyses and case-control studies confirmed an elevated risk of HZ infection and reactivation in SLE patients compared to age-matched individuals with non-inflammatory musculoskeletal conditions.[17]

In this study, 7 cases of cancer were discovered, including 4 cases of breast cancer (3.8%), 1 case of lung cancer (0.9%), 1 case of nasopharyngeal cancer (0.9%), and 1 case of renal cell carcinoma (0.9%). A recent study indicated a strong correlation between HZ and diminished immune function, a factor associated with the emergence of malignancies such as melanoma and bladder cancer. Although HZ may be connected to the onset of certain cancers, including lymphoid and endocrine malignancies, it is not associated with all cancer types. Additionally, this study revealed an even higher risk of certain cancers within the PHN group.[18] This study found 3 cases of asthma as a risk factor for HZ, with 2 females and 1 male (2.9%). Studies have explored the link between corticosteroid use and HZ risk in chronic obstructive pulmonary disease (COPD) patients.[19] The immunosuppressive nature of inhaled and oral corticosteroids may heighten infection susceptibility by impacting cellular immunity.[19] Another study also reported that the association between asthma and the risk of HZ was attenuated after adjusting for inhaled corticosteroids.[8]

In this study, 3 patients received hemodialysis as a risk factor for HZ, 1 female and 2 males (2.9%). This data is supported by the study that dialysis was an independent risk factor for zoster lesions. There were 33 out of 47 cases (70.21%) treated with dialysis and 46.81% of the control group, respectively. The extensive cohort study yielded comparable findings, revealing that patients undergoing peritoneal dialysis and hemodialysis exhibited a greater incidence of HZ than those without chronic renal disease.[20] In this study, it was discovered that drug hypersensitivity was a risk factor for HZ in 3 patients (1.9%). There seems to be a distinct connection between the reactivation of herpes viruses and drug hypersensitivity. Whether herpes

viruses directly trigger drug hypersensitivity or if it is a consequence of immune disruption caused by the reactivated viruses is not clear. Nevertheless, viral reactivation could play a role in the symptoms of the illness, potentially hindering disease recovery.[21] This study only found 1 patient (0.9%) with cholesterol as a HZ risk factor. However, a significantly higher risk of HZ was discovered among patients who used statins as a cholesterol treatment compared to non-users.[22] Conversely, there was no correlation between cholesterol as a risk factor for HZ. Statins can reduce levels of some proinflammatory cytokines and inhibit T-cell activation and proliferation, both of which may affect HZ susceptibility. According to one study, statins can increase the number of regulatory T cells (Tregs) in the body.[22] However, this increase in Tregs may cause latent viral infections like the VZV to reactivate.[22]

This study only found 1 patient (0.9%) with CKD as a risk factor for HZ, which is in line with a study reported that CKD was a risk factor for HZ infection.[23] Individuals with CKD are regarded as having a compromised immune status due to a blend of deficiencies in both innate and adaptive immune responses. This condition may be linked to reduced activation and performance of T cells, B cells, monocytes, and macrophages, along with a decrease in lymphokine synthesis and antibody-mediated cytotoxicity.[23]

In this study, 2.3% of patients had human immunodeficiency virus (HIV) positivity. Being exposed to immunotoxins and immunosuppressive medications poses additional potential risk factors. Furthermore, the use of immunosuppressive drugs and radiotherapy significantly increases the risk of HZ, especially among older individuals.[5] Another study discovered that HZ was present in 2% of HIV patient cases, which supports the findings of this study.[3] It occurs more frequently in older people and those with cellular immunodeficiency.[3] This study discovered that only 1 pregnant patient (0.9%) had a risk factor for HZ. Pregnancy-related HZ development is uncommon, but it does happen occasionally. Furthermore, a recent study found that women who received general anesthesia for cesarean delivery had a higher risk of HZ than women who received regional anesthesia.[11] Another study found that chronic infection or reactivation, or HZ, is not linked to fetal infection.[5] Varicella during pregnancy may cause disease in the fetus and complications in the newborn.[5]

This study revealed that only 1 patient (0.9%) had tuberculosis as a risk factor for HZ. A study explained that individuals with pulmonary TB had an elevated risk of developing HZ compared to those without pulmonary TB.[24] Stress is a potential trigger for the reactivation of VZV. Chronic pain related to the musculoskeletal system, the urogenital system, and endocrine disorders have all been related to stress that can lead to the development of HZ. Pulmonary TB might serve as a stressor for affected individuals, potentially leading to the onset of HZ.[24] Most complications in HZ patients at Dr. Soetomo General Academic Hospital, Surabaya, Indonesia, were found to be without complications in 78 patients (74.3%). Following that, the most common complication was PHN, which affected 19 patients (18.1%). Furthermore, there were 7 patients (6.7%) who experienced complications of secondary bacterial infection. Moreover, this study discovered that the older population was predisposed to problems, including PHN.[1]

This study found that PHN affected 19 patients (18.1%), consisting of 7 females and 12 males. According to a study, PHN is the most concerning complication of HZ infection in elderly individuals, commonly called shingles.[25] It is linked with various acute manifestations and symptoms, including a skin rash, nerve injury, and pain.[25] Data on secondary bacterial infection as a complication of HZ found 7 patients, 3 males and 4 females (6.7%). This study has the same pattern as the previous study. Secondary bacterial infections from zoster rash are possible. However, they are uncommon. Around the lesion, increasing erythema, tenderness, or purulence may indicate secondary infection.[1] In this study, only 1 patient (0.9%) got Ramsay Hunt syndrome as a complication of HZ. A study stated that the reactivation of the virus leads to the manifestation of "zoster" or "HZ".[26] This condition is characterized by pain and a vesicular rash following the path of the affected nerve, usually confined to a single dermatome. The specific symptoms and their distribution are contingent upon the nerve affected. Fewer than 1% of zoster cases involve the facial nerve, which can lead to Ramsay Hunt syndrome. It has been noted that HZ accounts for up to 30% of Ramsay Hunt syndrome cases.[26]

A comparison of different viewpoints and research outcomes related to HZ offers a nuanced understanding of this viral infection. Various studies may present divergent perspectives on risk factors, such as age, immunocompromised states, and underlying medical conditions, each shedding light on different aspects of susceptibility and severity. For example, while some studies may underscore advancing age as a primary risk factor due to waning immunity, others might highlight the heightened risk in individuals with conditions like HIV/acquired immunodeficiency syndrome (AIDS) or those undergoing immunosuppressive therapy. Furthermore, contrasting research outcomes regarding the efficacy of vaccines in preventing HZ and its complications can inform public health strategies and vaccination programs. Additionally, disparities in outcomes related to PHN, the most common complication of HZ, may stem from variations in pain management approaches, patient populations, and follow-up durations. By synthesizing these diverse viewpoints and research findings, clinicians and policymakers can develop comprehensive strategies for preventing, managing, and mitigating the burden associated with HZ.[4]

**Strength and Limitations**

This study has several strengths. Firstly, it provided valuable insights into the prevalence and risk factors associated with HZ, offering a comprehensive analysis of a substantial sample size (105 cases) over two years. The retrospective study design allows for examining historical data from medical records, providing a practical and cost-

effective approach to investigating the subject. However, certain limitations should be considered. The single-center focus of the study at Dr. Soetomo General Academic Hospital, Surabaya, Indonesia, might limit the generalizability of findings to broader populations. Furthermore, the study predominantly relied on quantitative data, potentially overlooking qualitative aspects that could provide a more nuanced understanding of patient experiences and outcomes. Despite these limitations, this study offers valuable contributions to the knowledge of HZ in a hospital setting. Future research endeavors may benefit from addressing these limitations to enrich the knowledge in this field further.

## Conclusion

Herpes zoster shows a higher prevalence among females, primarily associated with hypertension as the key risk factor, leading to PHN as the predominant complication. Despite its limitations, this study provided a comprehensive understanding of Herpes zoster demographics, nerve lesion distribution, risk factors, and complications within the specified hospital setting.

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## Conflict of Interest

The authors declared there is no conflict of interest.

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## Ethical Clearance

This study had received ethical clearance from the Health Research Ethics Committee Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia (No. 1192/LOE/301.4.2/I/2023) on 11/20/2023.

## Authors' Contributions

Conceived the research and prepared the draft of the manuscript by SKN. SKN gathered data and conducted a literature review. The SKN performed statistical analyses. ANH, MB, and AM supervised the results and discussions. All authors reviewed and approved the final version of the manuscript.

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