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The relationship of various risk factors to the incidence of Herpes Zoster at PKU Muhammadiyah Gamping Hospital

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ABSTRACT

Shingles (HZ) is reactivation of the Varicella zoster virus which is characterized by dermatomal vesicular lesions and unilateral pain. HZ cases have increased in recent decades, especially in people with weak immune systems, such as the elderly and women. To determine the relationship between various risk factors and the incidence of HZ at PKU Muhammadiyah Gamping Hospital in 2020 – 2022. Analytical observational research method with a cross-sectional design. Data source from medical records of PKU Muhammadiyah Gamping Hospital in 2020 - 2022 using total sampling method. The research subjects were HZ patients. Cases of contact dermatitis were used as a comparison. The number of HZ patients >64 years (31.2%), women (57.5%), with diabetes (9.7%), hypertension (22.1%), asthma (1.9%), heart disease (5 .2%), and other skin diseases (26%). There was a relationship between age (p=0.00), diabetes (p=0.03), hypertension (p=0.00), and other skin diseases (p=0.00) with HZ. There was no relationship between gender (p = 0.10), asthma (p = 0.68), heart disease and HZ (p = 1.00).Age, diabetes, hypertension, and other skin diseases were significantly associated with HZ, whereas gender, asthma, and heart disease were not associated with HZ.

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INTRODUCTION

Herpes Zoster (HZ) is a disease that is triggered by reactivation of the Varicella Zoster Virus (VVZ) after a primary infection that attacks the skin and mucosa (Hidayat et al., 2020). After primary infection, VVZ remains latent in the sensory ganglion cells of the spinal cord, then after some time the virus will experience reactivation along the sensory nerves and onto the skin (Kornia & Karmila, 2020). A disturbance in cellular immunity is said to be one of the factors that contributes to VVZ reactivation (Pusponegoro, et al., 2014).

Infection in HZ patients is characterized by vesicular lesions distributed according to the dermatome and unilateral radicular pain (Jannah & Yulisna, 2020). Initially, the lesion is maculopapular with an erythematous base which will develop into vesicles - pustules and then

harden after 7 - 10 days and heal within 2 - 4 weeks (John & Canaday, 2017). The pain felt can affect daily activities, such as decreasing the ability to do work so that the patient's quality of life may be disrupted (Bardach, et al., 2021).

The incidence of HZ has reportedly increased globally over the last few decades (John & Canaday, 2017). Global estimates of the incidence rate of HZ in Europe, Asia, and North America in the general population aged at least 50 years are 2.9 to 10.9 cases in 1000 population annually (San Martin et al., 2023). Research conducted by the Indonesian Herpes Study Group (KSHI) in 2011 - 2013 in several teaching hospitals in Indonesia showed that the peak of HZ cases in Indonesia occurred in patients aged 45 - 64 and was dominated by female patients (Pusponegoro, et al., 2014).

The risk of developing HZ increases with age, especially in someone who experiences suppressed cellular immunity due to certain diseases (Koshy, et al., 2018). Several risk factors for HZ that have been identified to date include old age, diabetes, genetic susceptibility, female gender, psychological stress, and European ethnicity (Kim, et al., 2018).

The prevalence of HZ in older people is still quite high. Although deaths due to HZ have never been reported in Indonesia, in patients with severe symptoms it can cause a decrease in quality of life. Therefore, further research is needed, especially in the DI Yogyakarta area, regarding the incidence of HZ and related risk factors so that it is hoped that prevention and management efforts can be improved.

RESEARCH METHOD

This study used an analytic observational method with a cross-sectional design. This study was conducted from April to June 2023 in the medical records department of PKU Muhammadiyah Gamping Hospital. In this study, contact dermatitis cases were used as a comparison because it is a non-infectious disease that has similar risk factors to HZ, but different clinical manifestations. The population used in this study were patients with HZ and contact dermatitis who were examined or treated at PKU Muhammadiyah Gamping Hospital in 2020-2022. The sampling method used was total sampling, namely by taking all data on HZ and contact dermatitis patients who were examined or treated in 2020-2022.

Inclusion criteria were all HZ and contact dermatitis patients examined or treated at PKU Muhammadiyah Gamping Hospital in 2020-2022 and patients with independent variable data, namely age, gender, and comorbidities available. Exclusion criteria were incomplete data on the independent variables of HZ patients in medical records. All data were analyzed through the process of editing, coding, and tabulating on SPSS..

RESULTS AND DISCUSSIONS

Results

In this study, there were 308 research subjects consisting of 154 HZ patients and 154 contact dermatitis patients who met the inclusion and exclusion criteria.

Characteristics of Research Subjects

Table 1. Characteristics of research subjects

Subject Characteristics	Frequency (n)	Percentage (%)
Age		
<5 years	12	3.9
5-14 years	8	2.6
15-24 years old	40	13.0
25-44 years old	65	21.1
45-64 years old	87	28.2
>64 years	96	31.2

Subject Characteristics	Frequency (n)	Percentage (%)
Amount	308	100
Gender		
Man	131	42.5
Woman	177	57.5
Amount	308	100
Concomitant Diseases		
DM		
Yes	30	9.7
No	278	90.3
Amount	308	100
HT		
Yes	68	22.1
No	240	77.9
Amount	308	100
Asthma		
Yes	6	1.9
No	302	98.1
Amount	308	100
Heart disease		
Yes	16	5.2
No	292	94.8
Amount	308	100
Other Skin Diseases		
Yes		
No	80	26
	228	74
Amount	308	100

Based on the table above, it is known that the majority of patients at PKU Muhammadiyah Gamping Hospital are >64 years old (31.2%), female (57.5%), and have comorbidities, such as DM (9.7%), HT (22.1%), asthma (1.9%), heart disease (5.2%), and other skin diseases (26%).

The relationship between various risk factors and the incidence of HZ at PKU Muhammadiyah Gamping Hospital

Table 2. Relationship between age and the incidence of HZ at PKU Muhammadiyah Gamping Hospital

Age	Incident HZ		Amount	*p value*
	Yes	No		
<5 years	0 (0.0%)	12 (3.9%)	12 (3.9%)	0,000
5-14 years		3 (1.0%)	8 (2.6%)	
15-24 years old	5 (1.6%)	29 (9.4%)	40 (13.0%)	
25-44 years old		44 (14.3%)	65 (21.1%)	
45-64 years old	11 (3.6%)	31 (10.1%)	87 (28.2%)	
>64 years	21 (6.8%)	35 (11.4%)	96 (31.2%)	
	56 (18.2%)			
	61 (19.8%)			
Amount	154 (50%)	154 (50%)	308 (100%)	

Based on the results of the analysis using the Lambda Contingency Coefficient statistical test, the p value = 0.000 (p value <0.05) was obtained, which means there is a relationship between age and the incidence of HZ at PKU Muhammadiyah Gamping Hospital.

Table 3. Relationship between gender and the incidence of HZ at PKU Muhammadiyah Gamping Hospital

Type Sex	Incident HZ		Amount	*p value*
	Yes	No		
Man	58 (18.8%)	73 (23.7%)	131 (42.5%)	0.106
Woman	96 (31.2%)	81 (26.3%)	177 (57.5%)	

Amount	154 (50%)	154 (50%)	308 (100%)

Based on the results of the analysis using the Chi-square statistical test, the p value = 0.106 (p value >0.05) was obtained, which means there is no relationship between gender and the incidence of HZ at PKU Muhammadiyah Gamping Hospital.

Table 4. Relationship between DM comorbidities and the incidence of HZ at PKU Muhammadiyah Gamping Hospital

DM	Incident HZ		Amount	*p value*
	Yes	No		
Yes	21 (6.8%)	9 (2.9%)	30 (9.7%)	0.033
No	133 (43.2%)	145 (47.1%)	278 (90.3%)	
Amount	154 (50%)	154 (50%)	308 (100%)	

Based on the results of the analysis using the Chi-square statistical test, the p value = 0.033 (p value <0.05) was obtained, which means there is a relationship between DM comorbidities and the incidence of HZ at PKU Muhammadiyah Gamping Hospital.

Table 5. Relationship between comorbidities with HT and the incidence of HZ at PKU Muhammadiyah Gamping Hospital

HT	Incident HZ		Amount	*p value*
	Yes	No		
Yes	46 (14.9%)	22 (7.1%)	68 (22.1%)	0.001
No	108 (35.1%)	132 (42.9%)	240 (77.9%)	
Amount	154 (50%)	154 (50%)	308 (100%)	

Based on the results of the analysis using the Chi-square statistical test, the p value = 0.001 (p value <0.05) was obtained, which means there is a relationship between HT comorbidities and the incidence of HZ at PKU Muhammadiyah Gamping Hospital.

Table 6. Relationship between comorbidities with asthma and the incidence of HZ at PKU Muhammadiyah Gamping Hospital

Asthma	Incident HZ		Amount	*p value*
	Yes	No		
Yes	4 (1.3%)	2 (0.6%)	6 (1.9%)	0.684
No	150 (48.7%)	152 (49.4%)	302 (98.1%)	
Amount	154 (50%)	154 (50%)	308 (100%)	

Based on the results of the analysis using the Chi-square statistical test, the p value = 0.684 (p value >0.05) was obtained, which means there is no relationship between asthma comorbidities and the incidence of HZ at PKU Muhammadiyah Gamping Hospital.

Table 1. The relationship between comorbid heart disease and the incidence of HZ at PKU Muhammadiyah Gamping Hospital

Heart Disease	Incident HZ		Amount	*p value*
	Yes	No		
Yes	8 (2.6%)	8 (2.6%)	16 (5.2%)	1,000
No	146 (47.4%)	146 (47.8%)	292 (94.8%)	
Amount	154 (50%)	154 (50%)	308 (100%)	

Based on the results of the analysis using the Chi-square statistical test, the p value = 1.000 (p value >0.05) was obtained, which means there is no relationship between comorbid heart disease and the incidence of HZ at PKU Muhammadiyah Gamping Hospital.

Table 2. Relationship between comorbidities and other skin diseases with the incidence of HZ at PKU Muhammadiyah Gamping Hospital

Other Skin Diseases	Incident HZ		Amount	*p value*
	Yes	No		
Yes	12 (3.9%)	68 (22.1%)	80 (26%)	0,000
No	142 (46.1%)	86 (27.9%)	228 (74%)	
Amount	154 (50%)	154 (50%)	308 (100%)	

Based on the results of the analysis using the Chi-square statistical test, the p value = 0.000 (p value <0.05) was obtained, which means there is a relationship between comorbidities with other skin diseases and the incidence of HZ at PKU Muhammadiyah Gamping Hospital. Apart from that, the correlation strength value obtained was r = -0.415, which means it has a moderately significant relationship and a minus value means it has the opposite relationship, namely if there is another skin disease then it is not HZ.

Discussion

Based on the results of research conducted at PKU Muhammadiyah Gamping Hospital on HZ patients who were examined or treated in 2020 – 2022, 154 patients were found. These figures show that the incidence of HZ in the DI Yogyakarta region, especially Gamping, is still quite high compared to other regions in Indonesia.

This is in line with research conducted by Hidayat, et al. (2020) which shows that there were only 18 patients at the Skin and Venereology Polyclinic at RSUP Dr. M. Djamil Padang 2015 – 2017. Apart from that, other research conducted by Alim, et al. (2022) at Ibnu Sina Hospital Makassar in 2016 – 2017 also showed that only a few patients were diagnosed with HZ, namely 25 patients.

The high and low levels of HZ cases in various regions of Indonesia vary. This may be due to the fact that each person's immune system is different. Apart from that, differences in ability to access health services in various regions of Indonesia can also influence the number of patients diagnosed with HZ.

The results of this study show that there is a relationship between age and the incidence of HZ and it is known that the majority of patients are elderly patients aged >64 years. These results are not much different from research conducted byCadogan, et al. (2022)which shows that there is a relationship between age and the incidence of HZ with p value = 0.000 (p value <0.05) and the average age of the study population is 51 years.

As a person gets older, a person's immune system will experience a gradual decline, this condition is usually called immunosenescence (Curran, et al., 2023). With VZV reactivation, the body will respond by stimulating CD4+ cells to release cytokines and stimulating IgG-mediated memory B cells, stimulating T helper cells to activate neutrophils and macrophages which can phagocytose VZV, and stimulating IL-2 to stimulate CD8+ to releaseIFN-γ, lysine, and protease to destroy viruses. However, in elderly patients there is a decrease in specific T cell immunity so that the risk of developing HZ will increase (Marra, et al., 2020).

The results of this study showed that there was no relationship between gender and the incidence of HZ and it was dominated by female patients. This is in line with research conducted by Alim, et al. (2022) which shows that the incidence of HZ most often occurs in women (56%). In contrast to research that has been carried out by Cadogan, et al. (2022) which shows that there is a relationship between female gender and the incidence of HZ with p value = 0.010 (p value <0.05)

and OR (95% CI) = 1.21, which means that the tendency for women to suffer from HZ is 1.21 times greater than men - man.

Women are more susceptible to VZV reactivation, presumably because women have more frequent contact with children who are infected with varicella (Ulum, et al., 2023). Apart from that, hormonal changes during the menopausal transition also affect women's immune responses (Cadogan, et al., 2022). One of the main female sex hormones is estrogen. Estrogen secretion plays a role in stimulating the first antiviral immune response, namely IFN-1. Estrogen levels during the menopausal transition period will decrease so that the risk of contracting viral infections, such as HZ, will increase (Harding & Heaton, 2022).

The results of this study indicate a relationship between DM comorbidities and the incidence of HZ. These results are in accordance with research that has been carried out by Marra, et al. (2020) which shows that there is a relationship between DM and the incidence of HZ with p value <0.0001 (p value <0.05) and RR (99.50% CI) = 1.24.

Increasing glucose levels can also result in decreased production of TNF-α and IFN-γ by T cells which function as antivirals. This condition is thought to be the cause of weak macrophage and leukocyte activity, causing someone with a high glycemic index to be susceptible to viral infections or other pathogens (Berbudi, et al., 2020).

The results of this study indicate a relationship between comorbidities of HT and the incidence of HZ. This is in line with research conducted bySoegiyono (2019)in Surabaya in 2016 – 2017 which stated that most HZ patients came with HT comorbidities (34.5%).

Patients with HT are more susceptible to HZ because when they are hypertensive, regulatory T cells work by suppressing the activation of innate and adaptive immune responses. Regulatory T cells will also produce immunosuppressive cytokines, such as TGF-β and IL-10 (Agita & Thaha, 2017). HT drugs, such as spironolactone, can also reduce Th17 activation (Singh, et al., 2014).

The results of this study show that there is no relationship between asthma comorbidities and the incidence of HZ. This lack of relationship may be partly due to the small number of HZ patients who have comorbid asthma, namely only 4 people.

This research is not in line with research conducted by Marra, et al. (2020) which shows that there is a relationship between asthma and the incidence of HZ with p value <0.0001 (p value <0.05) and RR (97.30% CI) = 1.24. Safonova, et al. (2023) found that the incidence of asthma is often associated with an imbalance of Th1 and Th2 immunity. Low Th1 immunity results in chronic atopic and inflammatory disorders, thereby increasing the risk of HZ.

The results of this study show that there is no relationship between comorbid heart disease and the incidence of HZ. In this study, only 8 HZ patients with heart disease were found (5.2%). The small number of patients could possibly be one of the reasons for the absence of this relationship.

Different research has been carried out by Marra, et al. (2020) which shows a relationship between cardiovascular comorbidities and the incidence of HZ with p value <0.0001 (p value <0.05) and RR (97.50% CI) = 1.34 Another study conducted by Boyalla, et al. (2023) shows several cardiovascular diseases, such as myocardial infarction, atherosclerosis, arrhythmia, heart valve disease, pericardial disease, cardiomyopathy, and heart failure indicating dysregulation of the innate immune system, such as neutrophils, monocytes, and macrophages. If there is dysregulation of the immune system, the body's defenses will decrease, making it susceptible to viral infections, such as VZV.

The results of this study indicate a relationship between comorbidities with other skin diseases and the incidence of HZ. Other skin diseases in question, such as atopic dermatitis and tinea.

This research is in line with research conducted by Wu, et al. (2023)which states that patients with atopic dermatitis have a higher risk of developing HZ than patients who do not

experience atopic dermatitis. The use of certain biological drugs, such as corticosteroids, which have immunosuppressive side effects, can affect the response of atopic dermatitis patients to HZ infection. Other research shows that the relationship between HZ and tinea is that HZ often occurs at the location of the tinea. This may be related to the theory of T cell exhaustion due to dermatophyte antigens that persist for a long time, resulting in a decrease in specific T cell effector function (Mathur, et al., 2023).

CONCLUSION

Based on research entitled "The Relationship of Various Risk Factors to the Incident of Herpes Zoster at PKU Muhammadiyah Gamping Hospital in 2020 - 2022" it can be concluded thatage, diabetes, hypertension, and other skin diseases were significantly associated with HZ, whereas gender, asthma, and heart disease were not associated with HZ.It is recommended that the results of this study can be used as material for medical consideration to improve efforts to prevent and better manage recurrence considering that HZ cases in the DI Yogyakarta area, especially Gamping, are still quite high.

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