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## ORIGINAL ARTICLE

## Clinical and economic burden of herpes zoster and postherpetic neuralgia in patients from the National Skin Centre, Singapore



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## ABSTRACT

**Background/Objectives:** There is a scarcity of recent data on the burden of herpes zoster (HZ) and postherpetic neuralgia (PHN) in Southeast Asia. We evaluated the prevalence, demographics, and disease burden of HZ and PHN in patients aged  $\geq 50$  years seen at a tertiary dermatological referral center, the National Skin Centre (NSC), Singapore.

**Methods:** We carried out a retrospective cohort analysis of NSC patient electronic medical records spanning >3 years from January 2010 to March 2013. Data on patient demographics, clinical characteristics, and medical management were collected.

**Results:** A total of 347 cases of HZ or PHN were included in this study. The mean age was 66.5 years with equal proportions of men and women. The majority of patients (85.6%) were of Chinese ethnicity. Patients presented to the NSC at various disease stages including acute HZ (83.0%), subacute HZ (10.7%), or PHN (6.3%). The most commonly affected anatomic site was thoracic dermatome (41.2%) and the most common prodromal symptom was pain (81.8%). In addition, pain was present in various stages of HZ, and it was the most unbearable symptom experienced during illness (85.5%). Patients in the older age group were more likely to suffer from pain for  $\geq 6$  months than patients in the younger age group. Most of the patients received antiviral treatment including acyclovir (70.9%) and valaciclovir (13.5%). Among all the patients, 85.0% received analgesia with the most common drugs being amitriptyline (25.4%) and gabapentin (21.9%). PHN led to significantly higher economic burden with a total cost of 414.69 Singapore dollars per patient versus 267.26 Singapore dollars for a non-PHN patient.

**Conclusion:** HZ and PHN cause a significant clinical and economic burden in Singapore.

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## Introduction

Herpes zoster (HZ), also called shingles, is a common infection caused by the reactivation of varicella-zoster virus (VZV) that is latent in the spinal and cranial sensory ganglia from the time of primary VZV infection (chickenpox).<sup>1–4</sup> A vesicular skin rash in the

affected dermatome, commonly accompanied by acute pain, characterizes the acute phase of HZ. HZ is associated with pain, which occurs in various disease stages, either preceding, associated with, following, or enduring for several weeks after the HZ skin eruption. The most frequent debilitating complication is postherpetic neuralgia (PHN).<sup>5–9</sup> PHN may persist for years and is often refractory to treatment.<sup>6</sup>

The incidence and severity of HZ and PHN increase with age, and is associated with a progressive decline in cell immunity to VZV.<sup>10–12</sup> Antiviral medication, if given early in acute HZ, is able to reduce the severity and duration of the acute blistering eruptions, but has not been found to prevent the development of PHN.<sup>4,8</sup> The zoster vaccine, Zostavax (Merck, USA), has been shown to decrease

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significantly the incidence and severity of HZ and PHN among older patients.<sup>13–16</sup> Zostavax has been approved for use in Singapore for adults aged  $\geq 50$  years of age since 2008. Studies on the prevalence and disease burden of HZ and PHN have been published from different countries including Australia,<sup>17</sup> Italy,<sup>18</sup> Taiwan,<sup>19</sup> France,<sup>20</sup> Germany,<sup>21</sup> Thailand,<sup>22</sup> Belgium,<sup>23</sup> the United Kingdom,<sup>24</sup> Spain,<sup>25</sup> Sweden,<sup>26</sup> and South Korea.<sup>27</sup> The most recent study on disease burden of HZ and PHN in Singapore dates back to 1997.<sup>28</sup>

## Methods

We carried out a retrospective cohort study of patients diagnosed as having HZ or PHN in the National Skin Centre (NSC) who were aged  $\geq 50$  years from 2010 to 2013. The NSC is the largest public dermatology clinic in Singapore, with >1200 attendances/d. Clinical data and detailed treatment history were retrieved from electronic medical records. Data of demographics, presenting stage, anatomic site involvement, prodrome, impact of illness, treatment including antiviral medication and analgesics, comorbidities, and disease burden including economic burden due to HZ and PHN were analyzed.

The diagnosis of HZ was based on the characteristic clinical presentation of a dermatomal blistering eruption. Zoster-associated pain was defined as prodromal (pain occurring before the onset of blistering eruptions), acute pain (pain within 1 month of onset), subacute pain (pain within 1 month to 3 months of onset), and PHN (pain appearing or persisting 3 months after the onset of blistering eruptions).

Costs were presented in Singapore dollars (S\$). In 2013, S\$1 was equal to approximately US\$0.8. The overall economic burden due to HZ included healthcare cost and indirect costs. Healthcare cost was calculated as the sum of total treatment cost, consultation fees, and hospitalization fees. Indirect cost due to absenteeism from work was calculated as the number of days of medical leave (taken by patients aged  $\leq 65$  years) multiplied by daily wage quoted from the Comprehensive Labour Force Survey (2012),<sup>29</sup> from which the daily wage of S\$160.6 was estimated from a monthly income of S\$3480.

This study was approved by the National Healthcare Group Domain Specific Review Board ethics committee. Statistical analysis was performed using SAS version 9.2 (SAS Institute Inc., Cary, NC, USA). Descriptive statistics were generated for all variables in the study. The two-sided *t* test was used to testify the difference in group means at the 5% significance level.

There was an average of 150–200 HZ patients seen in the NSC each year from 2003 to 2012 with the majority being of Chinese ethnicity. Based on the age distribution data of HZ from 2003 to 2012, we focused this study on those patients aged  $\geq 50$  years who were seen during period from January 2010 to March 2013.

## Results

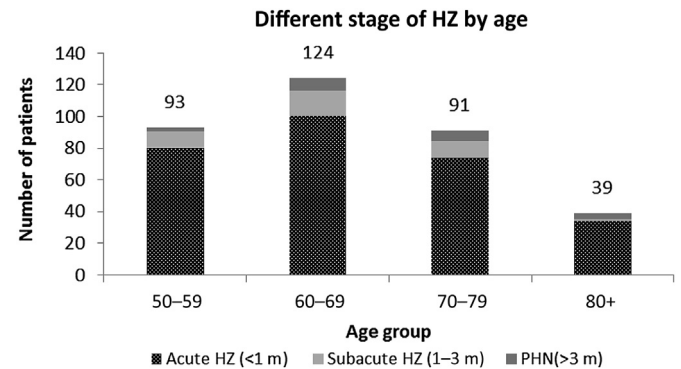
A total of 347 patients were included in this study. Table 1 shows the demographic data of our study cohort. The majority were Chinese (85.6%) with a small number of Malay, Indian, and other ethnicities (4.9%, 4.6%, and 4.9% retrospectively). These proportions reflected the general ethnic distribution in Singapore. Approximately half of the patients (50.6%) were women. The mean age of patients with HZ in our cohort was 66.5 years.

Because the NSC is a tertiary dermatological referral center, most of the patients would have sought treatment at either primary care or the emergency department before their first consultation, and therefore presented at the NSC in various stages of HZ. In this study, the majority of patients presented as acute HZ (83.0%), followed by subacute HZ (10.7%) and then PHN (6.3%; Figure 1).

**Table 1** Number and percentage of herpes zoster patients by age, sex, and ethnicity seen in the Singapore National Skin Centre from January 2010 to March 2013.

Age (y)	50–59	60–69	70–79	80+	Total
Male	53 (15.3)	61 (17.6)	43 (12.4)	15 (4.3)	172 (49.6)
Female	40 (11.5)	63 (18.2)	48 (13.8)	24 (6.9)	175 (50.4)
Chinese	73 (21.0)	112 (32.3)	76 (21.9)	36 (10.4)	297 (85.6)
Malay	8 (2.3)	3 (0.9)	5 (1.4)	1 (0.3)	17 (4.9)
Indian	6 (1.7)	4 (1.2)	6 (1.7)	0 (0.0)	16 (4.6)
Others	6 (1.7)	5 (1.4)	4 (1.2)	2 (0.6)	17 (4.9)
Total	93 (26.8)	124 (35.7)	91 (26.2)	39 (11.2)	347 (100.0)

Data are presented as n (%).

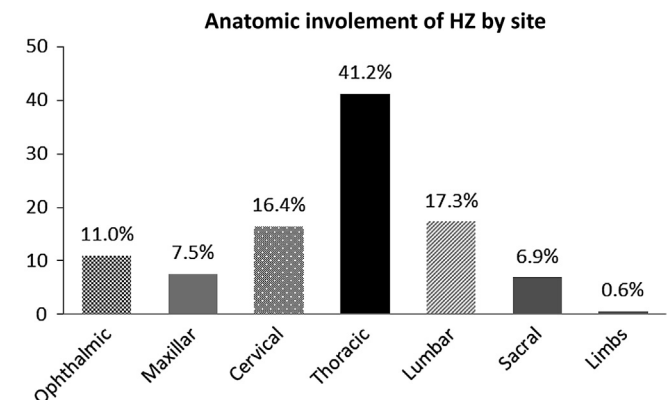


**Figure 1** Stage of herpes zoster (HZ) stratified by age.

The frequency of the anatomic involvement of HZ is shown in Figure 2. The thoracic (41.2%) region was the most commonly affected region in our patients. Other common affected regions were the lumbar (17.3%), cervical (16.4%), ophthalmic (11.0%), maxillary (7.5%), and sacral (6.9%) regions, and the limbs (0.1%).

Most of our patients experienced prodromal symptoms. In this study, the various prodromal symptoms were pain, itch, and insomnia (81.8%, 15.9% and 4.3% respectively). After onset of HZ, patients reported that the most unbearable symptoms experienced were pain or discomfort (85.9%), blistering rashes followed by scarring (44.4%), and insomnia or sleep disturbance (4.0%).

Table 2 shows that the majority of patients (84.4%,  $n = 293$ ) in this study received antiviral treatment, most commonly with acyclovir (70.9%). Approximately 55.6% of patients required treatment for pain control; the most commonly used medications were amitriptyline (25.4%), gabapentin (21.9%), tramadol (16.4%), paracetamol (13.5%), and oral nonsteroidal anti-inflammatory drugs (7.8%; Table 2). Due to the significant impact of pain on patients'



**Figure 2** Anatomic involvement of herpes zoster by site.

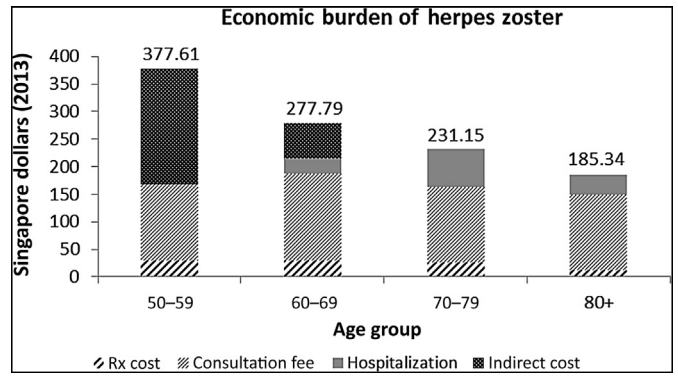
**Table 2** Antiviral treatment and analgesia treatment for herpes zoster.

Antiviral treatment	No. of patients	%
Acyclovir	246	70.9
Valaciclovir	47	13.5
Total	293	84.4
Analgesia treatment	No. of patients	%
Amitriptyline	88	25.4
Gabapentin	76	21.9
Tramadol	57	16.4
Paracetamol	47	13.5
Oral NSAIDs	27	7.8
Total	295	85.0

NSAIDs = nonsteroidal anti-inflammatory drugs.

quality of life, we further stratified the duration of pain by age groups (Figure 3). Approximately 78.0% of patients presenting with PHN were aged ≥ 60 years. Older patients were more likely to suffer pain for >6 months and their pain was more severe. The percentage of patients suffering pain for >6 months were 2.2%, 2.4%, 6.5%, and 7.7% in the age groups of 50–59 years, 60–69 years, 70–79 years, and ≥ 80 years, respectively.

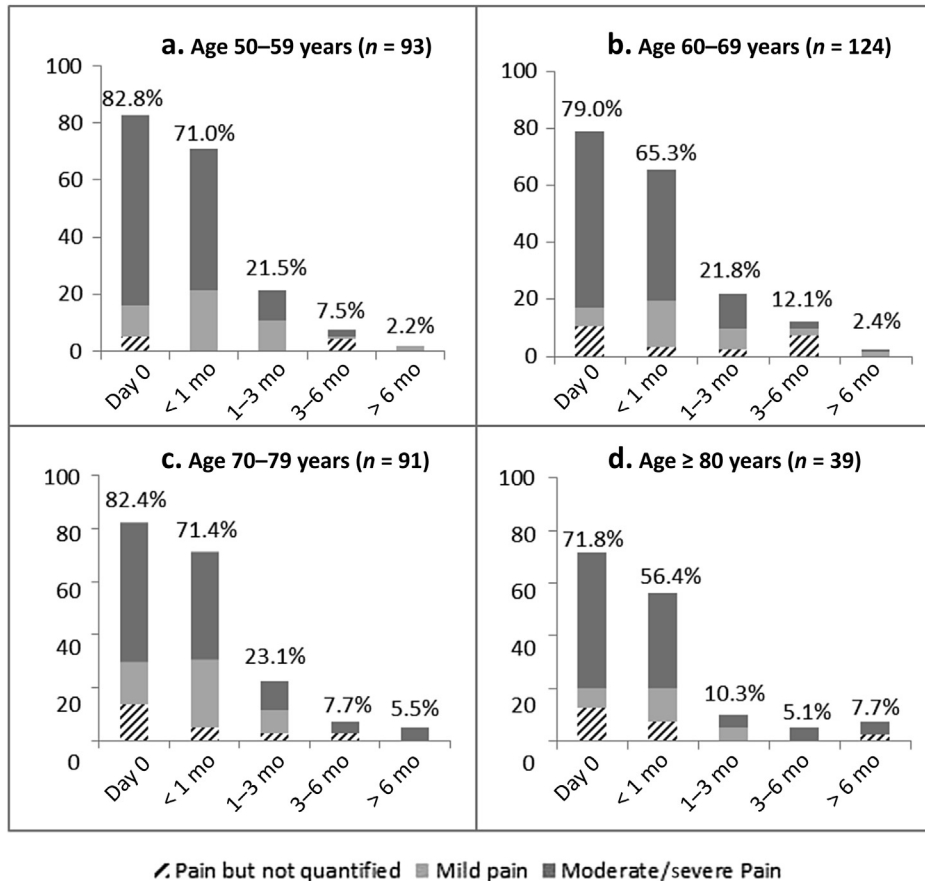
The overall economic burden caused by HZ includes treatment cost including antiviral and analgesia, consultation fee, hospitalization cost, and indirect cost due to absenteeism from work. The overall costs were highest in the labor productive age group, due to increased significant indirect costs because of absenteeism from work. The indirect costs were highest in the age group 50–59 years (\$\$ 210.56) followed by the age group 60–69 years (\$\$63.98; Figure 4).



**Figure 4** Economic burden of herpes zoster.

Our data showed that comorbidities such as diabetes, hypertension, dyslipidemia, and ischemia heart disease were common in patients. The prevalence of diabetes and ischemia heart disease was highest in the age 70–79 years group (23.1% and 8.8%, respectively). The prevalence of both hypertension and hyperlipidemia was highest in the age > 80 years group (51.3% and 36%, respectively).

Our study showed that PHN resulted in significantly higher costs. The mean direct cost including prescription, consultation, and hospitalization for PHN patients was S\$359.48 whereas the mean direct cost for non-PHN patients was S\$186.70. The difference in direct cost between patients with and without PHN, S\$172.78, can be considered as the additional cost driven by PHN.



**Figure 3** Duration of herpes zoster-related pain stratified by age group.

**Table 3** Comparison of economic burden (Singapore dollars) between postherpetic neuralgia (PHN) and non-PHN.

Economic burden/patient characteristics	PHN (n = 32)	Non-PHN (n = 315)
Total medication cost	47.53	23.99
Consultation fees (incl. government subsidy)	253.26	133.76
Hospitalization cost (incl. government subsidy)	58.69	28.95
Total direct cost	359.48	186.7
Total indirect cost (productivity loss)	55.21	80.56
Total cost (direct + indirect)	414.69	267.26

\*The *t* test shows the difference in the direct cost between PHN and non-PHN patients is 172.8 Singapore dollars at the 5% significance level (*p* = 0.008).

In general, an individual episode of HZ costs Singapore society S\$340, including pharmaceutical treatments, consultation provided by medical professionals, hospitalization, and productivity loss due to the absenteeism from work. It might, therefore, be more costly to treat HZ than the cost of prevention or early diagnoses and treatment. Moreover, patients with PHN incurred 1.92 times more costs than non-PHN patients; this was statistically significant (Table 3).

## Discussion

Our study shows that HZ is a debilitating disease causing significant clinical and economic burden to patients in Singapore. PHN led to significantly higher costs with a total cost of S\$414.69/patient compared with S\$267.26 for a non-PHN patient with HZ. One known HZ study from Singapore in 1997 showed that HZ tended to affect the older age groups and PHN was significantly more common in elderly patients.<sup>28</sup> This study provides updated knowledge related to the burden of herpes zoster in Singapore. Cost analysis including direct and indirect costs was not studied in the previous published paper.<sup>28</sup>

In this study, 84.4% of patients received early antiviral treatment. Early antiviral treatment, preferably within 72 hours of onset, reduces the severity and duration of the acute blistering eruptions. It is therefore important to train general practitioners to recognize the early symptoms and signs of HZ in order for the antivirals to be administered early. Patients should also be educated to identify the prodromal symptoms and skin eruptions related to HZ, and to seek early medical attention.<sup>4,8</sup>

Our study showed that pain is the most debilitating HZ symptom and that pain occurs at each stage of the disease including the prodrome, acute, subacute, and PHN stage. Thus adequate pain control should be administered at all stages of HZ. In this study, approximately 85% of patients in this study received analgesia.

Although both antivirals and analgesia are important, they can be expensive. Besides the expenses from medication and consultation fees, other costs include hospitalization cost for severe cases requiring inpatient care and indirect cost due to absenteeism from work. In our study, indirect cost was estimated as the number of days of medical leave multiplied by daily wage quoted from official statistics for patients aged  $\leq 65$  years (retirement age in Singapore is 65 years). Overall costs were highest in the working age group, due to increased significant indirect costs related to work absenteeism.

Our study showed that elderly patients were more likely to suffer from pain for >6 months. Approximately 78% of the patients presenting with PHN were aged  $\geq 60$  years. Previous studies have also indicated that older adults had a significantly higher risk of developing PHN.<sup>11–13</sup> In light of the growing elderly population in Singapore (by 2050, approximately 49% of Singaporeans will be aged 65+ years) and increased HZ prevalence increasing with age, the finding of greater severity of illness and longer pain duration in older patients is highly important.

This study had several limitations. Data were collected only from NSC electronic medical records, and not from primary physicians. Additional healthcare costs and days of medical leave may have been obtained from the general practitioner. Estimations of median income and government subsidies were obtained from the Comprehensive Labour Force Survey 2012<sup>29</sup> and may not be applicable to all patients. The impact of *presenteeism* or reduced productivity while at work due to discomfort and pain was difficult to quantify, but also represents an increased indirect cost.

This study provides a better understanding of the burden of HZ and PHN in patients aged  $\geq 50$  years. HZ and PHN were found to be common and debilitating diseases. Patients aged  $\geq 60$  years were particularly at an increased risk of severe and long-lasting pain which often affects health-related quality of life and daily activities. The overall costs were highest in the working age group, due to increased significant indirect costs as a result of work absenteeism.

The zoster vaccine has been reported to reduce morbidity from HZ and PHN markedly among older patients.<sup>13–16</sup> The significant clinical and economic burden of HZ indicated in our study underscores the importance of HZ vaccination in high-risk patients, especially for elderly adults who have higher HZ risk and are more likely to suffer from chronic zoster-associated pain.

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