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Report

Herpes zoster-associated severity and duration of pain, health-related quality of life, and healthcare utilization in Taiwan: a prospective observational study

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Abstract

Background To assess the severity and duration of herpes zoster (HZ)-associated pain (ZAP) and its impact on quality of life (QoL) and healthcare utilization (HCRU) from a patient perspective in routine care in Taiwan.

Methods A prospective, observational, single-cohort study was conducted in five centers across Taiwan. Patients were recruited at different time points during their HZ episode and were followed for ≤180 days. ZAP was assessed with the Initial Zoster Impact Questionnaire and the Zoster Brief Pain Inventory, QoL with the EQ-5D, and HCRU with a simple questionnaire.

Results A total of 150 patients were included with a mean age of 64.9 years and mean time since rash onset of 18.8 days. Prodromal pain was experienced by 64.7% of patients, of whom 91.8% reported moderate-to-severe pain. At enrollment, 98.0% of patients experienced ZAP. Mean ± SD worst pain score decreased from 5.95 ± 3.09 at enrollment to 2.65 ± 2.98 at 30 days and 0.28 ± 0.83 at 180 days. Postherpetic neuralgia was observed in 20.7% of patients. Mean ± SD EQ-5D score significantly decreased ($P < 0.001$) from 0.91 ± 0.16 before rash onset to 0.67 ± 0.18 after rash onset, showing significant QoL deterioration up to 60 days. The impact of HZ on QoL and pain severity was similar across age groups. Significant HCRU was observed including visits to the doctor (83.3% of patients), specialist (30.7%), emergency department (24.7%), physiotherapist (23.3%), and hospitalizations (20.7%).

Conclusion Severe morbidity and significant HCRU are associated with HZ in Taiwan, supporting the need for early intervention and preventive strategies to reduce the HZ-associated burden of illness.

Introduction

Herpes zoster (HZ) is caused by reactivation of the varicella-zoster virus, which, as a primary infection, causes varicella (chickenpox) and is characterized by pain in the involved dermatome and a unilateral vesicular rash.[1] The incidence of HZ in North America and Europe has been reported to range from 3.2 to 3.7 per 1000 person-years.[1–5] A recent study using claims data from Taiwan's National Health Insurance (NHI) estimated the annual incidence of HZ in Taiwan to be 5.0 per 1000 person-years corresponding to a lifetime risk of developing HZ of 32.2%.[6] The risk of developing HZ is augmented with age; the highest increase occurs between 50 and 60 years

of age and steadily increases thereafter, reaching 11.8 per 1000 person-years in the age group of 70 years or older.[7,8] In accordance, the incidence rate is expected to rise with the rapidly aging population of Taiwan.

The course of HZ can be divided into four phases: prodrome, acute, subacute, and chronic.[9] The prodrome phase commonly occurs 1–5 days before the onset of HZ rash,[1] acute HZ occurs up to 30 days after rash onset,[10] whereas for patients who thereafter develop chronic disease, the subacute phase occurs 30–90 days after rash onset.[11] Although the blistering rash is the most distinctive feature of HZ, the most significant common complication of HZ is postherpetic neuralgia (PHN).[12–14] PHN is included among the most distressing and debilitating types of pain and is often defined as long-lasting pain that persists for ≥90 days after rash onset.[10] The chronic pain of PHN can persist for months or years after the acute disease phase.[13–18] The incidence, severity, and duration of PHN increases with age, particularly in adults aged 50 years and older.[19–21] The reported incidence and duration of PHN can vary markedly, primarily due to variations in the clinical definition of PHN, in the patient populations studied, and in the methods of surveillance.[22]

Both HZ and PHN have been associated with impaired patient quality of life (QoL) significantly affecting physical and emotional functioning and causing physical and emotional distress.[23–27] Prevention and treatment for HZ and PHN present a significant medical need. Despite the availability of antiviral agents to treat HZ and a plethora of medications and other therapies to help control the associated pain, HZ and PHN represent a large and growing medical problem among older adults.

Patient suffering, loss of ability for self-care, and the need for healthcare resource utilization (HCRU) all contribute to reduced patient QoL and an increased economic burden of HZ and PHN. Data on HZ-related burden of illness among Taiwanese patients are scarce. The purpose of this observational study was to describe prospectively the severity and duration of zoster-associated pain (ZAP), assess the impact on QoL, and determine the HCRU associated with HZ and PHN in Taiwan in a routine care clinical setting.

Materials and methods

Study design and participants

This study followed similar methods as those described in the MASTER (Monitoring and Assessing Shingles Through Education and Research).[28] This was a prospective observational study in which recruitment took place in the offices of general practitioners or specialists in five hospitals in Taiwan (Taipei, Changhua, Tainan, Kaohsiung, and Taichung), between September 2008 and December 2009. Incident cases were defined as patients recruited for a current HZ episode with a duration of ≤7 days since rash onset or start of ZAP. Prevalent cases were defined as patients enrolled in the course of an HZ episode lasting longer than seven days. Patients were recruited at different time points during the course of their disease, corresponding to the time of entry to the healthcare system, and their follow-up was based on the time elapsed since their zoster rash onset date. Eligible participants included patients with a physician confirmed diagnosis of HZ rash or ZAP, including acute pain or PHN at enrollment, a documented date of onset HZ rash in the patient chart, ≥50 years of age and capable of completing the study questionnaires in Mandarin. Key exclusion criterion was the presence of any medical condition that could interfere with the evaluations required by the study. On the day of enrollment, eligible patients signed an informed consent form. The study was approved by the local Institutional Review Boards, as required, and was conducted in accordance with the ICH Good Clinical Practice Guidelines and the World Medical Association Declaration of Helsinki.

Data collection

There were 10 patient assessments in total. The enrollment assessment was conducted at the physician's office, while the remaining nine assessments were conducted through self-administered questionnaires on days 7, 14, 21, 30, 60, 90, 120, 150, and 180 after rash onset. For prevalent cases, questionnaires were administered from the next closest time point relative to the start of the rash for a follow-up of 180 days, based on 30-day increments. At each assessment, patients were assessed for the intensity of ZAP, QoL, and HCRU.

Outcome measures

Pain measurements

The primary objective was the pain severity of HZ at various time points from the onset of the HZ rash. This was measured by the "worst pain in the last 24 hours" question in the Zoster Brief Pain Inventory (ZBPI).[29] The ZBPI uses an 11-point Likert scale from 0 (no pain) to 10 (pain as bad as you can imagine) to rate HZ pain in four ways (current, worst, least, average in the last 24 hours) and has shown to be a reliable and valid measure of zoster pain. The ZBPI also measures, on an 11-point Likert scale, the interference of HZ pain with seven activities of daily living: general activity, mood, walking ability, work, relation with others, sleep, and enjoyment of life.[29,30] Pain intensity was classified in the following categories: 0 = no pain, 1 and 2 = mild pain, 3–6 = moderate pain, 7–10 = severe pain.

Postherpetic neuralgia was calculated for the 6-month follow-up period and was defined as a "worst pain in the last 24 hours" score of ≥3 after ≥90 days since rash onset.

The Initial Zoster Impact Questionnaire (IZIQ) assesses pain in an area of shingles rash for duration, intensity, and

characteristics of pain. The IZIQ was used at the enrollment visit to assess the worst pain during the prodrome phase.

Quality of life measurements

Impact of zoster and/or ZAP on QoL was measured with the EuroQoL, a standardized instrument for use as a measure of health outcomes, providing a simple descriptive profile and a single index value for health status.[31] The EuroQoL, or EQ-5D, measures five domains, specifically mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, and uses a visual analogue scale. The visual analogue scale asks participants to rate their current health state on a scale from 0 (worst imaginable health state) to 100 (best imaginable health state).

Quality of life weighting was used to adjust population-specific preferences for the health states defined by the EQ-5D. For the purposes of this study, the Japan-specific weights, which are more representative of Eastern populations, were used.

Healthcare resource utilization

Patient-reported HCRU was assessed with a simple questionnaire that was administered at each follow-up assessment. The questionnaire was used to record visits to physicians or clinics, hospitalizations, use of other health-related services, including physiotherapy, nursing services, ambulance services, psychologists, rehabilitation, natural or alternative medicine, prescription medications, and over-the-counter medications during the period since the last visit.

Statistical analysis

Sample size calculations were based on the precision of the sample estimates related to the primary outcome, namely the pain severity of HZ for patients who still experience ZAP at various time points from the onset of the HZ rash. Based on the proportion of incidence cases in the Canadian MASTER study,[28] the proportion of patients experiencing clinically significant ZAP at 30, 60, 90, 120, and 180 days after the HZ rash onset,[12] and the standard deviation of BPI pain observed in non-cancer patients as a proxy,[32] a total of 150 patients were required to produce a meaningful level of precision, as measured by the half width of the 95% confidence interval ($\omega/2$).

Statistical analyses were carried out using SPSS 12.0 (SPSS Inc., Chicago, IL, USA) and SAS 9.1 (SAS Institute, Cary, NC, USA). Descriptive statistics were utilized to describe the study sample, including measures of central tendency (mean) and dispersion (standard deviation) for continuous variables and frequency distributions for categorical variables. The one sample *t*-test was used to evaluate the change in QoL between prior to rash onset and all subsequent assessments. Subgroup analysis by age groups (50–59, 60–69, ≥70) was performed for the association of age and QoL or worst pain score. Between-age groups differences in QoL and worst pain were assessed for statistical significance using one-way analysis of variance (ANOVA).

Results

A total of 150 eligible patients were enrolled in the study. Among these, 77 (51.3%) were incident cases while 73 (48.7%) were prevalent HZ cases. There were 36 (24.0%) patients that had their first follow-up assessment at seven days, 71 (47.3%) at 14 days, 23 (15.3%) at 21 days, 19 (12.7%) at 30 days, and one (0.7%) at 60 days, based on the time elapsed since their rash onset.

Table 1 summarizes the patient and clinical characteristics at enrollment. Among the 150 patients enrolled, 30.0% were from Taipei, 20.7% each from Changhua, Tainan, and Kaohsiung, and 8.0% were from Taichung. The mean (SD) age was 64.9 (9.2) years, 54.0% of patients were female, and the mean (SD) time since rash onset was 18.8 (78.3) days. The most common primary dermatome region for HZ was the thoracic region (43.8%), followed by the head region (24.7%). The majority (60.3%) of patients with rash at enrollment had >20 lesions in the primary and adjacent dermatomes. Topical agents were the most common initial HZ treatment (81.8%) followed by antiviral agents (60.8%), specifically valacyclovir (27.7%), acyclovir (25.7%), and famciclovir (11.5%). Pain was experienced by 64.7% of patients during the prodrome phase. Among these patients, the mean (SD) worst prodromal pain score was 6.2 (2.9) with the vast majority of patients (91.8%) experiencing moderate to severe pain (worst pain score ≥3).

The proportion of patients who reported pain due to HZ decreased from 95.3% at enrollment to 12.2% after 180 days of follow-up. The intensity of HZ-associated worst pain (no pain, mild pain, moderate pain, and severe pain) over time is shown in Figure 1. At enrollment, 47.3% of patients reported severe pain, 39.3% reported moderate pain, and 8.7% mild pain. By 180 days, 7.4% and 4.7% of patients were still experiencing mild and moderate pain, respectively. PHN was observed in 20.7% of the patients.

Table 2 summarizes the worst pain score and the patient QoL, as assessed with the ZBPI and EQ-5D questionnaires, respectively, over time by age categories. Pain severity was highest at the time of enrollment and decreased significantly during the first 14 days from rash onset (mean decrease from 5.95 at enrollment to 3.97 at 14 days). Further decrease in pain severity was observed by 180 days reaching a mean (SD) score of 0.28 (0.83). HZ incidence resulted in a significant reduction in patient QoL with the mean (SD) EQ-5D score decreasing from 0.91 (0.16) before HZ to 0.67 (0.18) at study enrollment. QoL

Table 1 Demographic and clinical characteristics (n = 150)

Patient characteristics	Mean ± SD or *n* (%)
City	
Taipei	45 (30.0)
Changhua	31 (20.7)
Tainan	31 (20.7)
Kaohsiung	31 (20.7)
Taichung	12 (8.0)
Age (years), mean (SD)	64.9 ± 9.2
Age categories (years)	
50–59	53 (35.3)
60–69	50 (33.3)
≥70	47 (31.3)
Female gender	81 (54.0)
Completed college or higher education	31 (20.7)
Employed,[a]	45 (30.0)
Immunocompromised	20 (13.3)
Days since HZ rash onset	18.8 ± 78.3
HZ primary dermatome region,[b]	
Thoracic	64 (43.8)
Head	36 (24.7)
Cervical	24 (16.4)
Lumbar	13 (8.9)
Sacral	8 (5.5)
No. of lesions in primary and adjacent dermatomes,[b]	
1–10	30 (20.5)
11–20	28 (19.2)
21–50	47 (32.2)
> 50	41 (28.1)
Worst pain category	
No (0)	7 (4.7)
Mild (1–2)	13 (8.7)
Moderate (3–6)	59 (39.3)
Severe (≥7)	71 (47.3)
Worst prodromal pain score,[c]	6.2 ± 2.9
No pain (0)[c]	1 (1.0)
Mild pain (1–2)[c]	7 (7.2)
Moderate pain (3–6)[c]	41 (42.3)
Severe pain (≥7)[c]	48 (49.5)
Activity of daily interference ≥5	
Sleep	80 (53.3)
Mood	80 (53.3)
Enjoyment of life	73 (48.7)
General activity	64 (42.7)
Normal work	61 (40.7)
Relations with other people	54 (36.0)
Walking ability	44 (29.3)
Problems in EQ5D health domains[d]	
Having pain or discomfort	127 (84.7)
Being anxious or depressed	97 (64.7)
Usual activities	53 (35.3)
Mobility	43 (28.7)
Self-care	39 (26.0)
Mean number of prescription HZ medications[e]	6.3 ± 4.7
Mean percentage pain relief provided by treatments or medications[f]	46.6 ± 28.5
Previous and concomitant treatment of HZ[g]	
Topical agent	121 (81.8)
Antiviral medication[h]	90 (60.8)
Acetaminophen	81 (54.7)
NSAID/aspirin	69 (46.6)
Opiates	27 (18.2)
Antidepressants	26 (17.6)
Antiepileptics	25 (16.9)
Anxiolytics	22 (14.9)
Ophthalmic agent	20 (13.5)
Alternative medicine	20 (13.5)
Antibiotics	16 (10.8)
Steroids	12 (8.1)

HZ, herpes zoster; NSAID, nonsteroidal anti-inflammatory drug; SD, standard deviation.
[a]Full time or part time.
[b]Proportions based on 146 patients with presence of HZ rash at baseline.
[c]Calculated among 97 patients who reported prodromal pain. Level of pain ranges on a scale from 0 (no pain) to 10 (pain as bad as you can imagine).
[d]Problems include level 2 and level 3 responses from EuroQoL questionnaire.
[e]Prescription medications represent those currently taken within the last 2 weeks before patient enrollment (including those used for HZ).
[f]The level of pain relief ranges on a scale from 0% (no relief) to 100% (complete relief).
[g]Patients may have reported more than one treatment. Data were available for 148 patients.
[h]Antiviral medications received were acyclovir (n = 38), valacyclovir (n = 41), and famciclovir (n = 17).

improved thereafter reaching an almost perfect health status by 180 days (mean [SD] EQ-5D = 0.96 [0.11]). However, the impact of HZ on patient QoL remained significant until 30 days from rash onset as indicated by the statistically lower EQ-5D score compared to before the onset of HZ (P = 0.001). Based on the minimally important difference in EQ-5D reported by Walters and Brazier, the impact of HZ on QoL was clinically important until 21 days of follow-up.[33] The impact of HZ on QoL and pain severity was similar across all age groups at each visit. For patients 50–59, 60–69, and ≥70 years of age, the mean (SD) EQ-5D score at enrollment was 0.67 (0.15), 0.66 (0.19), and 0.68 (0.21), respectively, significantly increasing to 0.97 (0.11), 0.96 (0.10), and 0.93 (0.12) after 180 days from rash onset. A trend towards a higher worst pain score after 30 days from rash onset was observed for patients 70 years of age or older without, however, reaching statistical significance.

Figure 2 summarizes the mean interference of ZAP on patient activities of daily living over time. HZ pain significantly interfered with all dimensions measured by the ZBPI, however sleep, mood, and enjoyment of life were

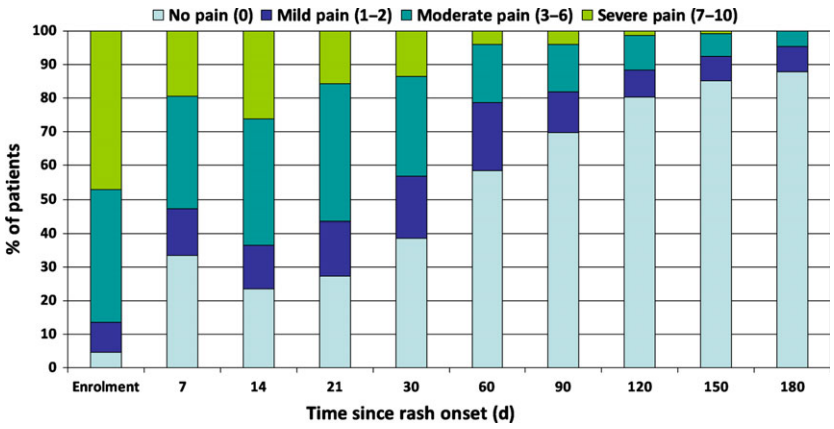

Figure 1 Herpes zoster-associated worst pain intensity in the last 24 h. Scores based on a rating scale of 0 (no pain) to 10 (pain as bad as you can imagine). Pain intensity categories were classified as follows: 0 = no pain; 1 and 2 = mild pain; 3–6 = moderate pain; 7–10 = severe pain

Table 2 Worst pain score and EQ-5D score by age categories over time

				Age categories (years)						
		Total		50–59		60–69		≥70		
Parameter	**Visit**	***n***	**Mean ± SD**	***n***	**Mean ± SD**	***n***	**Mean ± SD**	***n***	**Mean ± SD**	***P* value[b]**
Worst pain in last 24 h[a]	Enrollment	150	5.95 ± 3.09	53	5.87 ± 3.13	50	6.16 ± 3.07	47	5.83 ± 3.14	0.846
	Day 7[c]	36	3.42 ± 3.32	14	3.36 ± 3.79	12	4.92 ± 2.61	10	1.70 ± 2.75	0.074
	Day 14[c]	107	3.97 ± 3.23	46	3.74 ± 3.21	34	4.35 ± 3.15	27	3.89 ± 3.46	0.699
	Day 21[c]	129	3.19 ± 2.87	50	2.98 ± 2.94	42	3.60 ± 2.75	37	3.00 ± 2.92	0.533
	Day 30[c]	148	2.65 ± 2.98	53	2.36 ± 2.73	50	2.70 ± 2.80	45	2.93 ± 3.45	0.631
	Day 60[c]	149	1.38 ± 2.16	53	1.11 ± 1.95	50	1.40 ± 2.15	46	1.65 ± 2.41	0.467
	Day 90[c]	149	1.04 ± 1.99	53	0.77 ± 1.59	50	1.12 ± 2.13	46	1.26 ± 2.26	0.454
	Day 120[c]	148	0.59 ± 1.47	53	0.45 ± 1.35	50	0.60 ± 1.51	45	0.76 ± 1.55	0.598
	Day 150[c]	148	0.42 ± 1.16	53	0.32 ± 0.96	50	0.24 ± 0.89	45	0.73 ± 1.54	0.087
	Day 180[c]	148	0.28 ± 0.83	53	0.13 ± 0.52	50	0.24 ± 0.89	45	0.49 ± 1.01	0.098
EQ-5D score	Before rash	150	0.91 ± 0.16	53	0.89 ± 0.21	50	0.91 ± 0.14	47	0.93 ± 0.12	0.535
	Rash onset	150	0.67 ± 0.18	53	0.67 ± 0.15	50	0.66 ± 0.19	47	0.68 ± 0.21	0.805
	Day 7[c]	35	0.83 ± 0.17	13	0.80 ± 0.18	12	0.80 ± 0.18	10	0.90 ± 0.13	0.275
	Day 14[c]	107	0.78 ± 0.18	46	0.78 ± 0.17	34	0.79 ± 0.19	27	0.78 ± 0.18	0.972
	Day 21[c]	129	0.81 ± 0.20	50	0.83 ± 0.19	42	0.79 ± 0.18	37	0.83 ± 0.23	0.621
	Day 30[c]	148	0.85 ± 0.18	53	0.86 ± 0.18	50	0.84 ± 0.18	45	0.85 ± 0.18	0.892
	Day 60[c]	149	0.91 ± 0.15	53	0.92 ± 0.14	50	0.91 ± 0.16	46	0.89 ± 0.16	0.690
	Day 90[c]	149	0.92 ± 0.15	53	0.94 ± 0.11	50	0.91 ± 0.17	46	0.91 ± 0.14	0.443
	Day 120[c]	148	0.93 ± 0.15	53	0.96 ± 0.10	50	0.92 ± 0.19	45	0.91 ± 0.15	0.116
	Day 150[c]	148	0.95 ± 0.12	53	0.96 ± 0.11	50	0.95 ± 0.12	45	0.93 ± 0.13	0.358
	Day 180[c]	148	0.96 ± 0.11	53	0.97 ± 0.11	50	0.96 ± 0.10	45	0.93 ± 0.12	0.178

SD, standard deviation.
[a]The level of pain was rated on a scale from 0 (no pain) to 10 (pain as bad as you can imagine).
[b]Between-group *P* value was assessed with one-way ANOVA.
[c]Relative to the date of rash onset.

more highly affected (mean [SD] interference at baseline of 5.0 [3.8], 4.6 [3.3], 4.3 [3.6], respectively). The extent of interference significantly decreased over time in accordance with the relief in HZ pain (Table 2).

Herpes zoster-related HCRU after the shingles episode and during the 180-day observation period is summarized in Table 3. The most commonly utilized types of healthcare resources were visits made to the doctor's office (83.3% of patients) followed by visits to a specialist (30.7%), emergency room (24.7%), physiotherapist (23.3%), and hospitalizations (20.7%).

Discussion

To our knowledge, this is the first prospective cohort study in Taiwan to assess the severity and duration of

pain and healthcare utilization associated with HZ from the patient perspective. At study enrollment, more than 87% of patients experienced moderate to severe pain and discomfort, which was associated with a devastating physical and psychological impact, including anxiety and depression. After a 6-month follow-up period in our study, 12% of patients continued to experience mild to severe pain. In addition to outpatient primary care visits, a significant portion of the patients required visits to the emergency department, hospitalization, or frequent visits to a physiotherapist to mitigate pain.

Similar to previous studies in North America and Europe, approximately 65% of patients experienced prodromal pain, and more than 87% of patients experienced intense acute pain in the current study.[28,34–38] The impact of ZAP was substantial and apparent across all domains of QoL, particularly sleep, mood, and enjoyment of life. Although reported impact on general activities varies across studies, lack of sleep has been consistently reported to be one of the common types of interference.[26,37,39,40] The mean QoL EQ5D score was 0.67 at study enrollment and slightly increased to 0.85 after 30 days of follow-up. The reported QoL in this Taiwanese sample is comparable although slightly higher than that reported in a previous study in Canada (EQ5D score of 0.59 at baseline and 0.67 after 30 days of follow-up),[37] which is probably due to inclusion of prevalent HZ cases in the current study. Overall, the impact of HZ on QoL is comparable to that of chronic diseases such as diabetes mellitus, myocardial infarction, and clinical depression.[41,42]

A significant proportion (21%) of patients developed PHN, a debilitating and long-lasting pain, in this relatively old study population with mean age of 65 years. Similarly, a previous study using the Taiwan NHI database reported that the incidence of PHN was 15% in patients with HZ between 60 and 80 years of age and 20–30% in patients with HZ older than 80 years of age.[43] Furthermore, a retrospective chart review performed in Taiwan estimated the incidence of PHN to 34.1%, which was higher in older patients.[44] In addition to older age, greater severity of acute pain and prodromal pain are known risk factors for PHN,[45] which may have contributed to the different incidence of PHN observed in our study.

Table 3 Patient-reported HCRU after rash onset and during the 180-d observation period

Type of HCRU	*n* (%)	Mean number ± SD[b]
Visit to doctor's office[a]	125 (83.3)	6.0 ± 8.6
Visit to a specialist	46 (30.7)	2.8 ± 2.7
Visit to emergency room	37 (24.7)	1.3 ± 0.6
Visit to a physiotherapist/rehabilitation	35 (23.3)	13.5 ± 20.4
Hospitalization	31 (20.7)	5.6 ± 2.9
Admission to long-term care facility	2 (1.3)	3.5 ± 2.1
Nursing services	1 (0.7)	1.0 (NC)
Ambulance service	1 (0.7)	1.0 (NC)

HCRU, healthcare resource utilization; NC, not calculable.
[a]In addition to the enrollment assessment.
[b]Among patients who used the respective healthcare resource.

The current study also described the treatment patterns and healthcare utilization associated with HZ. In spite of the previously demonstrated efficacy of early administration of antiviral medications on reducing ZAP, antiviral medications were only prescribed in 61% of patients. Antiviral use may be uncommon in this population because treatment is not typically covered by insurance for most mild cases of HZ in Taiwan. In accordance with the severe burden of illness, significant HCRU was associated with the management of HZ, including visits to the doctor (83.3%), specialist (30.7%), emergency department (24.7%), and physiotherapist (23.3%), as well as hospitalizations (20.7%) over six months of follow-up. Overall, this study highlights the importance of

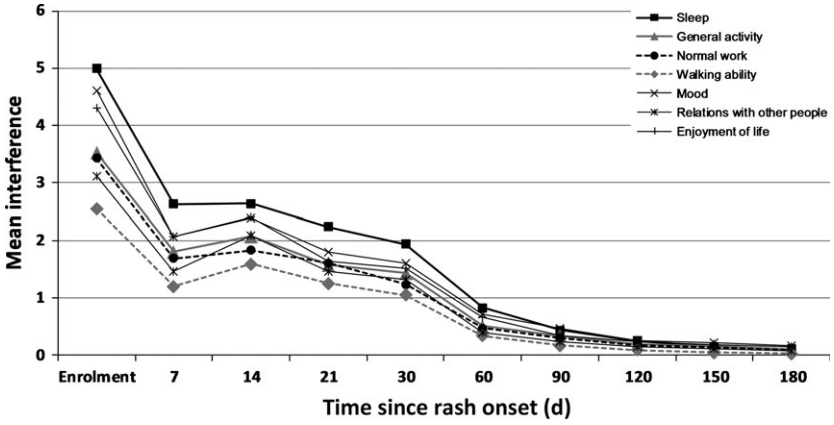

Figure 2 Interference of herpes zoster pain with daily activities

early diagnosis and treatment with antiviral medications and preventive measures.

The current study has several limitations. The study population included older patients (>50 years) who sought care for HZ. Therefore, participants may be composed of slightly more severe cases of HZ than in the general population. In addition to including incident cases, the present study also included prevalent cases, which may have led to recall bias. However, the majority of cases were incident, and the mean time since rash onset in this population was 19 days. Finally, to be eligible for the study, patients had to have a clinical diagnosis of HZ, and laboratory confirmation was not mandated, which may have resulted in misclassification of exposure.

In conclusion, the present study showed that severe morbidity and significant healthcare utilization was associated with HZ in Taiwan. The number of HZ and PHN cases is expected to increase in the coming years due to the steady increase in the elderly population. Early appropriate treatment for HZ and PHN and preventive measures should be considered to reduce the burden of disease.

Acknowledgments

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Conflicts of Interest and Source of Funding

RRW and CJA are employed by Merck & Co., Inc. KK is a post-doctoral fellow funded by Merck & Co., Inc. EP, ER and JSS are employees of JSS Medical Research the contract research organization that was hired to manage the study, conduct the data analysis, and co-ordinate the manuscript preparation. For the remaining authors, none were declared.

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