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Burden of illness, quality of life, and healthcare utilization among patients with herpes zoster in South Korea: a prospective clinical–epidemiological study

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SUMMARY

Objectives: To assess the herpes zoster (HZ) disease burden, including the severity and duration of HZ-associated pain, its impact on quality of life (QoL), and healthcare resource utilization (HCRU) in a South Korean clinical setting.
Methods: Patients aged ≥50 years were followed prospectively for ≤6 months. Based on the duration of their episode at enrolment, cases were classified as incident (<7 days) or prevalent (≥7 days). HZ pain and discomfort were measured with the HZ Severity of Illness (HZ-SOI) severity-by-duration composite score.
Results: One hundred fifty-one patients (69.5% prevalent cases) were enrolled. Prodrome pain was experienced by 68.2% of patients, of whom 95.1% experienced moderate-to-severe pain; post-herpetic neuralgia was experienced by 38.4%. Prevalent disease, higher acute pain, and older age were significant predictors of greater HZ-SOI, while use of antivirals was associated with decreased HZ-SOI. HZ-associated pain was associated with reduced QoL and affected all daily living activities (particularly mood, life enjoyment, general activities, and sleep), resulting in significant HCRU, including primary care doctor, specialist, or physiotherapist consultations, hospitalizations, and emergency department visits.
Conclusion: Severe morbidity, impaired QoL, and significant HCRU are associated with HZ in South Korea, especially in older patients, supporting the need for early intervention and preventive strategies to reduce the HZ-associated disease burden.

1. Introduction

In South Korea, the disease burden of herpes zoster (HZ), commonly known as shingles or zoster, has been considerably higher than that reported for other countries and has been increasing in the last 5 years; this increase could be related to an increase in longevity.[1] Adults and the elderly in particular are likely to suffer the debilitating effects and considerable levels of pain caused by the reactivation of varicella zoster virus (VZV), which, as a primary infection, produces chickenpox.[2–7]

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While the most distinctive feature of HZ is a unilateral, vesicular, cutaneous eruption with a dermatomal distribution,[4,7,3] the most frequently debilitating symptom is pain, which may occur during the prodromal phase, the acute eruptive phase, and the post-herpetic phase of the infection. Zoster-associated pain may persist for months or even years after the rash has healed,[8–11] diminishing the patient's quality of life (QoL) and functional capacity to a degree comparable to that in diseases such as congestive heart failure, myocardial infarction, diabetes mellitus type 2, and major depression.[4]

Despite the availability of a plethora of antiviral and other medications, it is difficult to adequately treat HZ and post-herpetic neuralgia. According to the guidelines of the International Herpes Management Forum, treatment with oral antiviral agents for 7 days is recommended for patients at risk of developing post-herpetic neuralgia (>50 years of age, severe acute pain, severe rash, or significant prodromal symptoms).[12] However, to be maximally effective, antiviral agents should be administered within 72 h of acute symptom onset, which is often not possible due to delays in patients seeking medical help or to delayed diagnosis.[12–14] Furthermore, even if timely therapy takes place, current treatments are effective in some patients, but may show limited benefit and poor tolerability in others,[15] especially those already taking other medications. Although treatment with antiviral agents accelerates cessation of viral shedding, hastens rash healing, and reduces the duration of acute pain,[16] a recent Cochrane review concluded that treatment with oral aciclovir does not have a significant impact on the incidence of post-herpetic neuralgia.[17] Similarly, another meta-analysis concluded that oral corticosteroids given acutely during HZ reactivation are ineffective in preventing post-herpetic neuralgia.[18] Recently, a vaccine against HZ was shown to reduce the HZ burden of illness by 61%, the incidence of post-herpetic neuralgia by 67%, and the incidence of HZ by 51%[19] in adults 60 years of age and older. Similarly, the recent Zostavax Efficacy and Safety Trial (ZEST) showed that zoster vaccination in patients aged between 50 and 59 years significantly reduces the incidence of HZ by 70%.[20] As such, these studies have demonstrated the efficacy of a zoster vaccine in significantly decreasing both the incidence and severity of HZ and post-herpetic neuralgia among older adults.

To date, data on the burden of HZ specific to South Korea are scarce.[1] The purpose of this prospective observational study was to measure the burden of illness due to HZ and post-herpetic neuralgia, assess their impact on QoL, and determine the associated healthcare resource utilization (HCRU) in South Korea. In addition to providing evidence of the medical need, the current study was done to inform the evidence-based decision-making process related to future vaccination policies in South Korea.

2. Methods

2.1. Study design

This study followed similar methods to those described in the MASTER (Monitoring and Assessing Shingles Through Education and Research) set of studies.[21] This was a 6-month, prospective, observational study in HZ patients recruited from the practices of 19 specialists (three infectious diseases specialists and 16 dermatologists) from the Korea University Guro Hospital (six investigators), the Kyung Hee University Medical Center (five investigators), and the Catholic University of Korea (eight investigators) between February 2009 and October 2010. The study was approved by the institutional review boards of the Korea University Guro Hospital, the Kyung Hee University Hospital, and the Catholic Medical Center (CMC) Clinical Research Coordination Center of the Catholic University of Korea. At recruitment, patients were assessed for eligibility and underwent a review of historical exposure to varicella, immune status, HZ characteristics, as well as a review of HZ medication and treatment use. Incident cases were defined as patients with a current HZ episode enrolled <7 days since rash onset or start of zoster-associated pain. Prevalent cases were defined as patients with a current HZ episode enrolled ≥7 days after rash onset or start of zoster-associated pain. For the incident cases, the baseline (day 0) and day 7 assessments were conducted in the physician's office, while the remaining eight assessments were conducted through telephone interview on days 14, 21, 30, 60, 90, 120, 150, and 180. For the prevalent cases, the baseline assessment took place in the physician's office and six follow-up assessments were completed by telephone interview at 30-day intervals for a total of 6 months.

2.2. Patient population

Male and female patients aged ≥50 years at the date of onset of HZ rash, with a physician-confirmed diagnosis of HZ, were eligible for the study. Additional inclusion criteria were: documented date of onset of HZ rash in the patient's chart and the ability to understand spoken and written Korean, to complete the study questionnaires, and to understand the study and the content of the informed consent form, as well as patient availability for the study follow-up period. Eligible patients provided informed consent prior to study enrolment.

2.3. Outcome measures

2.3.1. Pain measurements

The primary outcome was the burden of illness due to zoster-associated pain. This was measured with the HZ Severity of Illness score (HZ-SOI), a severity-by-duration composite measure of total pain and discomfort experienced by HZ patients. Pain severity was derived from the pain ratings obtained from the 'worst pain in the last 24 h' question of the Zoster Brief Pain Inventory (ZBPI).[22]

The Initial Zoster Impact Questionnaire (IZIQ) was used at the baseline visit to assess the worst pain during the prodrome phase. Post-herpetic neuralgia was defined as a score of ≥3 in the 'worst pain in the last 24 h' question of the ZBPI at ≥90 days after rash onset.

2.4. QoL measurements

QoL was measured with the EuroQoL (EQ-5D),[23] which measures five dimensions, specifically mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The EQ-5D has high validity and has demonstrated reliability across several health states. At the first visit, the EuroQoL questionnaire was completed by the patient twice to describe: (1) usual QoL without HZ or zoster-associated pain; (2) QoL in their current health state during their HZ episode. At each follow-up assessment, the EuroQoL questionnaire was completed once by the patient.

QoL 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 Asian populations, were used.

2.4.1. Healthcare resource utilization (HCRU)

HCRU was assessed by a simple questionnaire administered at each follow-up assessment. Patients were asked to record the HCRU related to their HZ rash or zoster-associated pain. HCRU included visits to physicians or clinics, hospitalizations, use of other health-related services including physiotherapy, nursing services, psychologists, rehabilitation, natural or alternative medicine, prescription medications, and over-the-counter medications, as well as diagnostic tests and procedures performed. Emphasis was placed on the use

of antiviral and analgesic medications. At the baseline visit, a review of HZ episode medications and treatments used was conducted. During the study follow-up, the zoster-related medication and treatment inventory was collected to obtain details, including type and estimated duration of HZ medications and treatments used. These included prescription medications, over-the-counter products, and other services used.

2.5. Statistical methods

Descriptive statistics were produced for all variables in the study. Measures of central tendency (mean) and dispersion (standard deviation (SD), 95% confidence interval) were produced for all continuous scale variables. Frequency distributions were produced for all categorical scale variables. In addition to the total study cohort, all analyses were stratified by prevalent and incident HZ cases.

For the assessment of the HZ-SOI during the study period, the area under the curve of worst pain severity over time after enrolment was calculated using the multiple segment trapezoidal rule for integration. To adjust for possible confounders, mixed models with repeated measures were used, where HZ-SOI throughout the follow-up period was the dependent variable and baseline characteristics were included as covariates. Mixed effects models assume both population characteristics (fixed effects) and individual-specific effects (random effects) and accommodate varying follow-up times with possible missing values. Covariates considered in the model were visit number, worst pain at baseline, age, immune status (impaired vs. normal), use of HZ medications, and total number of lesions in the primary and adjacent dermatomes. Impaired immune status was defined as the use of oral corticosteroids, immunosuppressive therapy, therapy for organ transplant, or chemotherapy for solid tumor, the presence of invasive cancer, HIV/AIDS infections, or a

Table 1
Patient demographics and baseline characteristics

Demographics and baseline characteristics	Cohort		Total cohort (n = 151)
	Prevalent cases (n = 105)	Incident cases (n = 46)	
Age, years, mean (SD)	64.1 (8.2)	62.7 (9.3)	63.6 (8.5)
Female gender, n (%)	60 (57.1)	33 (71.1)	93 (61.6)
Days since rash onset, mean (SD)	95.4 (323.4)	4.2 (1.5)	67.6 (272.5)
Employment status at baseline			
Full time	29 (27.6)	11 (23.9)	40 (26.5)
Part time	6 (5.7)	1 (2.2)	7 (4.6)
Retired	10 (9.5)	3 (6.5)	13 (8.6)
Unemployed	23 (21.9)	9 (19.6)	32 (21.2)
Home maker	33 (31.4)	20 (43.5)	53 (35.1)
Student	0 (0.0)	0 (0.0)	0 (0.0)
Other	4 (3.8)	2 (4.3)	6 (4.0)
Highest level of education, n (%)			
Primary/grade school	21 (20.0)	9 (19.6)	30 (19.9)
High school or equivalent	51 (48.6)	20 (43.5)	71 (47.0)
Community college	4 (3.8)	3 (6.5)	7 (4.6)
University or higher	10 (9.5)	7 (15.2)	17 (11.3)
No education	12 (11.4)	6 (13.0)	18 (11.9)
Missing	7 (6.7)	1 (2.2)	8 (5.3)
HZ primary dermatome region, n (%)			
Thoracic	34 (32.4)	25 (54.3)	59 (39.1)
Head	20 (19.0)	8 (17.4)	28 (18.5)
Lumbar	10 (9.5)	7 (15.2)	17 (11.3)
Cervical	12 (11.4)	5 (10.9)	17 (11.3)
Sacral	0 (0.0)	1 (2.2)	1 (0.7)
Missing	29 (27.6)	0 (0.0)	29 (19.2)
Ongoing HZ treatment, n (%)[a]			
NSAID or aspirin	57 (54.3)	31 (67.4)	88 (58.3)
Topicals	49 (46.7)	32 (69.6)	81 (53.6)
Antiviral medications	35 (33.3)	44 (95.6)	79 (52.3)
Aciclovir	6 (5.7)	13 (28.3)	19 (12.6)
Famciclovir	21 (20.0)	26 (56.5)	47 (31.1)
Valaciclovir	8 (7.6)	5 (10.9)	13 (8.6)
Anti-depressants	38 (36.2)	28 (60.9)	66 (43.7)
Anti-epileptics	44 (41.9)	15 (32.6)	59 (39.1)
Acetaminophen	42 (40.0)	14 (30.4)	56 (37.1)
Opiates	19 (18.1)	14 (30.4)	33 (21.9)
Anxiolytics	14 (13.3)	7 (15.2)	21 (13.9)
Antibiotics	12 (11.4)	5 (10.9)	17 (11.3)
Ophthalmologics	3 (2.9)	0 (0.0)	3 (2.0)
Steroids	3 (2.9)	0 (0.0)	3 (2.0)
Other	27 (25.7)	19 (41.3)	46 (30.5)
Worst pain during prodrome phase, VAS cm,[b] mean (SD)	5.45 (4.13)	4.85 (3.97)	5.27 (4.08)
Worst pain score, n (%)			
≥3	70 (66.7)	28 (60.9)	98 (64.9)
≥5	62 (59.0)	26 (56.5)	88 (58.3)

SD, standard deviation; HZ, herpes zoster; NSAID, non-steroidal anti-inflammatory drug; VAS, visual analog scale.

[a] A patient may have initiated more than one HZ treatment at baseline. Each patient was counted once per medication type. The percentage is based on the total number of patients in the study (N = 151) or on the respective incident (n = 46) and prevalent (n = 105) cohorts.

[b] Worst pain during the prodrome phase was assessed with the Initial Zoster Impact Questionnaire (IZIQ). The level of pain was rated on a VAS of 0 (no pain) to 10 (pain as bad as you can imagine). Information was missing for one incident case.

hematologic malignancy, or a low neutrophil or CD4 count. Backward selection of variables with $p < 0.05$ was used to identify the covariates to be kept in the final model.

Parameters affecting the HZ-SOI since rash onset were assessed using multiple regression analysis. Considering that each patient entered the cohort at a different time after rash onset and contributed to the HZ-SOI after that point, a Markov Chain Monte Carlo (MCMC) method was used to generate 1000 datasets with imputed missing values before the predictor assessment. The robustness of the model was examined by comparing the imputed and the observed HZ-SOI in patients with complete profiles.

Sample-size calculations were based on the precision of the sample estimates related to the zoster-associated pain severity in patients still experiencing pain at various time points from HZ rash onset. Based on the proportion of incident cases in the Canadian MASTER study,[21] the proportion of patients experiencing clinically significant zoster-associated pain at 30, 60, 90, 120, and 180 days after HZ rash onset,[19] and the standard deviation of BPI pain observed in non-cancer patients as a proxy,[24] a sample size of 150 patients would produce a standard error of the mean between ±0.23 and ±0.45 depending on the study visit. Statistical analyses were conducted with SPSS 12.0 (SPSS Inc., Chicago, IL, USA) and SAS 9.2 (SAS Institute, Cary, NC, USA).

3. Results

A total of 151 patients were enrolled in the study, of whom 46 (30.5%) were incident HZ cases and 105 (69.5%) were prevalent HZ cases. Table 1 summarizes the patient characteristics at baseline, overall and by type of cohort (prevalent vs. incident). The mean (±SD) age was 63.6 (±8.5) years and the majority of patients were female (61.6%). The mean time since rash onset was 67.6 days for the overall study population, 95.4 days for the prevalent cases, and 4.2 days for the incident cases. The most common documented primary dermatome region for HZ was the thoracic region (39.1%), followed by the head region (18.5%). At study enrolment, 58.3% were treated with a non-steroidal anti-inflammatory (NSAID) or aspirin and 52.3% with a topical agent, while the use of an antiviral agent was reported by 52.3% of patients. Pain had been experienced by 68.2% of patients during the prodromal phase. Of these patients, the vast majority (95.1%) experienced moderate to severe pain (worst pain score ≥3) during that period.

The intensity of HZ-associated worst pain by patient cohort over time is shown in Figure 1. Overall, the total HZ burden was higher in the prevalent cases compared to the incident cases during the study period. A significant ($p < 0.001$) decrease over time was observed in the HZ-SOI score in both patient subgroups; however, the rate of the decrease from peak was higher in the incident cases. Increased worst pain at baseline was associated with a greater HZ-SOI ($p < 0.01$). Furthermore, older age was identified as a predictor of greater HZ-SOI in the incident cases ($p < 0.001$). However, immune status at baseline, the use of HZ medications, and the number of lesions in the primary and secondary dermatome(s) did not have a significant impact on HZ-SOI. Post-herpetic neuralgia was reported in 38.4% of the total cohort: 46.7% of the prevalent cases and 19.6% of the incident cases.

When assessing the HZ-SOI since rash onset, older age, type of patient cohort, use of antiviral medications, and worst pain at rash onset were identified as significant independent predictors (Table 2). Upon mutual adjustment for all possible predictors, prevalent cases experienced a significantly higher burden of illness overall and during the acute (0–30 days) and sub-acute (30–90 days) phases. Patients 70 years of age or older also experienced greater HZ-SOI compared to patients aged between 50 and 59 years. A significant association between antiviral medication use and reduced burden of illness was observed overall and across all phases of the course of HZ. Finally, increased pain severity at rash onset predicted a greater HZ-SOI during the acute phase, but not the sub-acute and chronic phases.

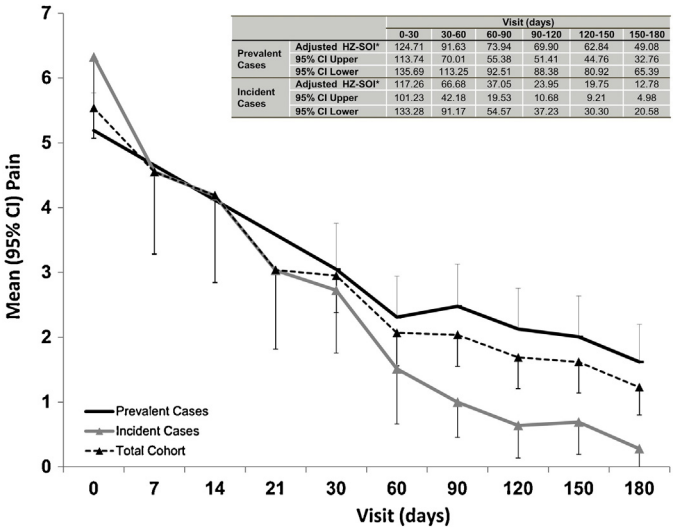

Figure 1. Worst pain in the last 24 h as measured with the Zoster Brief Pain Inventory (ZBPI) by incident and prevalent cases (HZ-SOI, Herpes Zoster Severity of Illness; CI, confidence interval).
*Least square mean estimate adjusted for all covariates retained in the model. For prevalent cases, the covariates retained in the model were the visit number and the worst pain at baseline. For incident cases, age was also retained. Additional covariates entered in the model, but not retained due to statistical non-significance, included immune status (normal vs. impaired), use of herpes zoster medications, and number of lesions in the primary and adjacent dermatomes.
†Prevalent cases did not complete the ZBPI at days 7, 14, and 21. Only one direction of the 95% CI is shown in the figure for visual clarity.

Table 3 summarizes the mean severity of least, average, and current pain over time as assessed with the ZBPI. Pain severity was highest at the time of recruitment and decreased significantly during the first 7 days in the incident cases (mean changes of −1.50, −1.56, and −1.78 in least, average, and current pain, respectively), or the first 30 days in the prevalent HZ cases (mean changes of −1.42, −1.73, and −1.88 in least, average, and current pain, respectively). A further decrease in the pain severity scores was observed by 180 days. By the end of the 180-day follow-up period, 24.1% of responders reported still having HZ-related pain.

The impact of zoster-associated pain on patient daily activities is shown in Figure 2. Zoster-associated pain was reported to have a significant impact on almost all dimensions measured by the ZBPI; however patient mood and enjoyment of life were affected the most.

Figure 3 summarizes the mean EQ-5D score over time. HZ incidence resulted in a significant reduction in patient QoL with the mean (SD) EQ-5D score decreasing from 0.91 (0.12) prior to HZ to 0.65 (0.16) after HZ onset. QoL improved thereafter, however the impact of HZ on patient QoL remained significant until 180 days of follow-up, as indicated by the statistically lower EQ-5D scores compared to prior to the onset of HZ. A similar trend was observed when looking at the subgroups of incident and prevalent cases. Of note, the mean (SD) EQ-5D score in the prevalent cases was consistently lower than that of the incident cases throughout the study period.

HZ-related HCRU after the shingles episode and during the 180-day observation period is summarized in Table 4. The most commonly utilized type of healthcare resource was visits to a primary care physician's office (98.7% of patients), followed by visits to a specialist (55.0%), hospitalizations (32.5%), visits to the emergency room (17.9%), and visits to a physiotherapist (15.2%). Among those who visited the primary care physician's office, patients visited an average of 7.0 times. Among those who required hospitalization, patients stayed in the hospital for an average of 8.9 days.

Table 2
Multivariate analysis assessing predictors of the herpes zoster severity-of-illness score (HZ-SOI)[a]

	$HZ\text{-}SOI_{0-180\ days}$			$HZ\text{-}SOI_{0-30\ days}$			$HZ\text{-}SOI_{30-90\ days}$			$HZ\text{-}SOI_{90-180\ days}$		
	Estimate	SE	*p*-Value	Estimate	SE	*p*-Value	Estimate	SE	*p*-Value	Estimate	SE	*p*-Value
Age, years												
50–59	Ref	-	-	Ref.	-	-	Ref.	-	-	Ref.	-	-
60–69	39.1	66.5	0.558	2.6	12.2	0.833	20.4	24.9	0.414	16.1	40.8	0.694
>70	159.1	79.6	0.048	12.8	14.6	0.382	63.0	29.7	0.036	83.2	49.1	0.093
Cohort												
Incidence cases	Ref.	-	-	Ref.	-	-	Ref.	-	-	Ref.	-	-
Prevalent cases	206.6	63.6	0.002	107.6	11.5	<0.001	88.1	23.8	<0.001	10.9	39.1	0.781
Worst pain score at rash onset												
Per unit of pain (0–10)	22.8	13.7	0.099	7.7	2.5	0.003	5.3	5.1	0.300	9.7	8.4	0.251
Number of lesions in primary/adjacent dermatomes												
1–10	Ref.	-	-	Ref.	-	-	Ref.	-	-	Ref.	-	-
11–20	99.3	80.6	0.220	8.3	15.1	0.584	40.6	30.3	0.182	50.4	49.4	0.309
21–50	47.3	73.0	0.518	1.5	13.4	0.913	4.5	27.2	0.869	41.3	44.9	0.360
>50	151.8	112.6	0.180	22.5	20.2	0.268	43.8	42.0	0.299	85.5	69.7	0.222
Antiviral medication												
No	Ref.	-	-	Ref.	-	-	Ref.	-	-	Ref.	-	-
Yes	−344.2	119.5	0.005	−53.4	25.0	0.036	−118.4	44.8	0.009	−172.4	72.6	0.019
Immune status												
Normal	Ref.	-	-	Ref.	-	-	Ref.	-	-	Ref.	-	-
Impaired[b]	25.0	100.2	0.803	7.9	18.0	0.660	3.8	37.2	0.918	13.3	61.9	0.831

SE, standard error; Ref., reference.
[a] The saturated models are shown for more information on the impact of possible predictors. Similar results were obtained upon excluding the non-significant covariates (number of lesions, immune status) from the models.
[b] Defined as use of oral corticosteroids, immunosuppressive therapy, therapy for organ transplant, or chemotherapy for solid tumor, presence of invasive cancer, HIV/AIDS infections, or hematologic malignancy, or low neutrophil or CD4 count.

4. Discussion

To our knowledge, this is the first study prospectively assessing the HZ burden of illness in South Korea. Overall, significant HZ-associated pain was observed over 180 days of follow-up after disease onset, which affected all activities of daily living and was associated with decreased QoL and increased HCRU.

Sixty-five percent of the patients experienced moderate to severe pain (worst pain of ≥3 on a 0–10 scale) during the prodromal phase, while 38.4% developed post-herpetic neuralgia, a debilitating and long-lasting pain. The higher incidence of post-herpetic neuralgia relative to that observed in other prospective studies in Canada and Thailand,[25,26] is probably due to the inclusion of both prevalent and incident cases of HZ (post-herpetic neuralgia incidence of 46.7% and 19.6%, respectively). In accordance, severity of illness was also significantly higher in prevalent cases. Alternatively, the participation of specialists may have resulted in the recruitment of more severe cases of HZ. Consistent with a previous study in Canada,[21] higher acute pain severity and older age were identified as predictors of greater severity of illness, while the use of antiviral medications was associated with decreased severity and duration of HZ-associated pain.

In light of the increasing proportion of the elderly population in South Korea (by 2050 South Korea is expected to be the world's second oldest population, with 35% of its population over 65 years of age)[27–29] and the fact that the HZ prevalence in South Korea is highest in individuals in their seventies,[1] the finding that greater HZ severity of illness was observed in older patients is highly important. Interestingly, older age predicted higher HZ-SOI only in the sub-acute and chronic phases, suggesting that younger and older cases are as likely to experience a significant burden of illness in the acute phase and that the effect of HZ is more chronic in elderly patients. This is in agreement with the fact that older cases are at a significantly higher risk of developing post-herpetic neuralgia.[30–33]

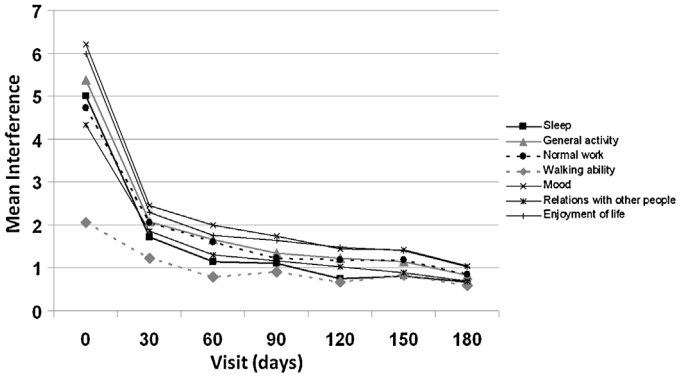

Figure 2. Interference of zoster-associated pain with daily activities. The level of interference was rated on a scale from 0 (no interference) to 10 (complete interference).

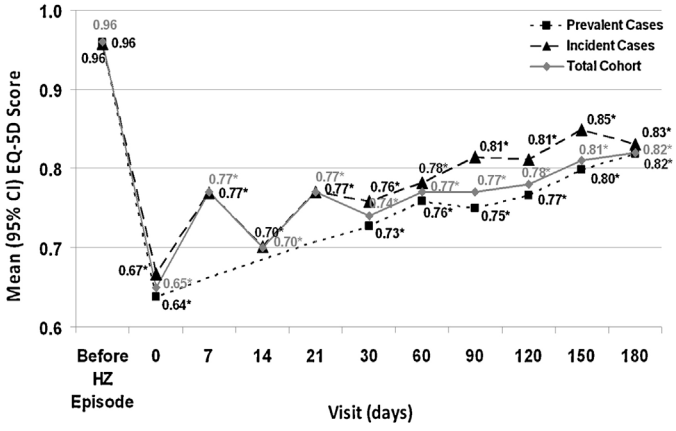

Figure 3. EuroQoL score over time by prevalent and incident cases.
*Statistically significant changes ($p < 0.05$) in EQ-5D score from before the herpes zoster episode.

Table 3
Zoster-associated pain over time[a]

Pain parameter	Visit (day)	Cohort								Total cohort ($N=151$)			
		Prevalent cases ($n=105$)				Incident cases ($n=46$)							
		n	Pain	Change from baseline		n	Pain	Change from baseline		n	Pain	Change from baseline	
			Mean (SD)	Mean (SD)	p-Value[b]		Mean (SD)	Mean (SD)	p-Value[b]		Mean (SD)	Mean (SD)	p-Value[b]
Least pain in last 24 h	0	104	2.77 (2.47)	NA	NA	46	3.07 (2.69)	NA	NA	150	2.86 (2.54)	NA	NA
	7	-	-	-	-	18	1.61 (1.88)	−1.50 (1.58)	0.001	18	1.61 (1.88)	−1.50 (1.58)	0.001
	14	-	-	-	-	27	1.56 (1.89)	−1.48 (3.24)	0.025	27	1.56 (1.89)	−1.48 (3.24)	0.025
	21	-	-	-	-	28	1.29 (1.65)	−1.64 (3.15)	0.010	28	1.29 (1.65)	−1.64 (3.15)	0.010
	30	93	1.27 (1.99)	−1.42 (2.54)	<0.001	40	1.10 (1.79)	−2.08 (3.16)	<0.001	133	1.22 (1.93)	−1.62 (2.75)	<0.001
	60	91	1.18 (1.91)	−1.38 (2.79)	<0.001	39	0.64 (1.27)	−2.49 (2.92)	<0.001	130	1.02 (1.76)	−1.71 (2.86)	<0.001
	90	93	1.11 (2.10)	−1.42 (3.00)	<0.001	40	0.20 (0.72)	−2.90 (2.82)	<0.001	133	0.83 (1.85)	−1.87 (3.01)	<0.001
	120	92	1.01 (1.91)	−1.52 (2.91)	<0.001	39	0.18 (0.68)	−2.95 (2.83)	<0.001	131	0.76 (1.68)	−1.95 (2.95)	<0.001
	150	94	0.95 (2.04)	−1.65 (2.78)	<0.001	39	0.10 (0.45)	−3.00 (2.80)	<0.001	133	0.70 (1.78)	−2.05 (2.84)	<0.001
	180	94	0.73 (1.71)	−1.86 (2.68)	<0.001	39	0.15 (0.71)	−3.00 (2.86)	<0.001	133	0.56 (1.51)	−2.20 (2.78)	<0.001
Average pain in last 24 h	0	104	3.94 (2.54)	NA	NA	46	4.74 (2.45)	NA	NA	150	4.19 (2.53)	NA	NA
	7	-	-	-	-	18	3.06 (2.13)	−1.56 (1.79)	0.002	18	3.06 (2.13)	−1.56 (1.79)	0.002
	14	-	-	-	-	27	3.11 (2.53)	−1.70 (3.34)	0.013	27	3.11 (2.53)	−1.70 (3.34)	0.013
	21	-	-	-	-	28	2.14 (2.24)	−2.54 (3.21)	<0.001	28	2.14 (2.24)	−2.54 (3.21)	<0.001
	30	93	2.19 (2.60)	−1.73 (2.76)	<0.001	40	1.95 (2.03)	−2.90 (3.03)	<0.001	133	2.12 (2.44)	−2.08 (2.88)	<0.001
	60	91	1.75 (2.46)	−2.02 (2.75)	<0.001	39	0.97 (1.78)	−3.85 (2.86)	<0.001	130	1.52 (2.30)	−2.57 (2.90)	<0.001
	90	93	1.89 (2.60)	−1.90 (3.07)	<0.001	40	0.70 (1.22)	−4.10 (2.55)	<0.001	133	1.53 (2.33)	−2.57 (3.08)	<0.001
	120	92	1.59 (2.41)	−2.21 (3.27)	<0.001	39	0.41 (1.02)	−4.41 (2.61)	<0.001	131	1.24 (2.16)	−2.87 (3.24)	<0.001
	150	94	1.62 (2.57)	−2.20 (3.13)	<0.001	39	0.54 (1.19)	−4.23 (2.41)	<0.001	133	1.30 (2.30)	−2.80 (3.07)	<0.001
	180	94	1.21 (2.25)	−2.63 (2.97)	<0.001	39	0.21 (0.73)	−4.64 (2.64)	<0.001	133	0.92 (1.98)	−3.23 (3.01)	<0.001
Current pain	0	104	3.61 (2.49)	NA	NA	46	4.09 (2.51)	NA	NA	150	3.75 (2.50)	NA	NA
	7	-	-	-	-	18	2.61 (2.23)	−1.78 (2.05)	0.002	18	2.61 (2.23)	−1.78 (2.05)	0.002
	14	-	-	-	-	27	2.81 (3.01)	−1.22 (3.68)	0.097	27	2.81 (3.01)	−1.22 (3.68)	0.097
	21	-	-	-	-	28	1.89 (2.39)	−2.00 (3.13)	0.002	28	1.89 (2.39)	−2.00 (3.13)	0.002
	30	93	1.69 (2.32)	−1.88 (2.68)	<0.001	39	1.33 (1.99)	−2.79 (2.66)	<0.001	132	1.58 (2.29)	−2.15 (2.70)	<0.001
	60	91	1.21 (2.30)	−2.23 (2.74)	<0.001	39	0.90 (1.50)	−3.13 (2.61)	<0.001	130	1.12 (2.09)	−2.50 (2.72)	<0.001
	90	93	1.63 (2.64)	−1.79 (3.11)	<0.001	40	0.65 (1.39)	−3.38 (2.71)	<0.001	133	1.34 (2.37)	−2.27 (3.07)	<0.001
	120	91	1.12 (2.19)	−2.33 (3.02)	<0.001	39	0.33 (0.84)	−3.69 (2.58)	<0.001	130	0.88 (1.92)	−2.74 (2.95)	<0.001
	150	94	1.34 (2.63)	−2.14 (3.22)	<0.001	39	0.54 (1.25)	−3.46 (2.79)	<0.001	133	1.11 (2.33)	−2.53 (3.14)	<0.001
	180	94	1.11 (2.27)	−2.40 (2.92)	<0.001	39	0.26 (0.91)	−3.79 (2.75)	<0.001	133	0.86 (2.01)	−2.81 (2.93)	<0.001

SD, standard deviation; NA, not applicable.
[a] The level of pain was rated on a scale from 0 (no pain) to 10 (pain as bad as you can imagine).
[b] p-Value was assessed with the one-sample t-test.

Table 4
Herpes zoster-associated healthcare resource utilization (HCRU) from rash onset to end of study

Type of healthcare resource	Cohort				Total cohort ($n=151$)	
	Prevalent cases ($n=105$)		Incident cases ($n=46$)			
	n (%)	Mean number ± SD[a]	n (%)	Mean number ± SD[a]	n (%)	Mean number ± SD[a]
Visit to primary care doctor's office	104 (99.0)	8.0 ± 8.2	45 (97.8)	4.7 ± 3.4	149 (98.7)	7.0 ± 7.2
Visit to a specialist[b]	61 (58.1)	5.5 ± 9.1	22 (47.8)	3.7 ± 3.8	83 (55.0)	5.0 ± 8.0
Hospitalization	34 (32.4)	8.6 ± 9.9[c]	15 (32.6)	9.4 ± 8.2[c]	49 (32.5)	8.9 ± 9.3[c]
Visit to emergency room	18 (17.1)	1.3 ± 0.6	9 (19.6)	1.3 ± 0.5	27 (17.9)	1.3 ± 0.5
Visit to a physiotherapist/rehabilitation	16 (15.2)	7.0 ± 14.3	7 (15.2)	9.3 ± 11.6	23 (15.2)	7.6 ± 13.4
Admission to long-term care facility	0 (0.0)	NA	2 (4.3)	3.5 ± 3.5[d]	2 (1.3)	3.5 ± 3.5[d]
Nursing services	1 (1.0)	9.0 (NC)	0 (0.0)	NA	1 (0.7)	9.0 (NC)
Ambulance service	2 (1.9)	1.0 ± 0.0	0 (0.0)	NA	2 (1.3)	1.0 ± 0.0
Psychiatrist/psychologist/counselor	2 (1.9)	1.0 ± 0.0	0 (0.0)	NA	2 (1.3)	1.0 ± 0.0

NC, not calculable; NA, not applicable.
[a] Among patients who used the respective healthcare resource.
[b] Except a physician or a dermatologist.
[c] Number of days spent in hospital; median of 6.0 days, 8.0 days, and 6.0 days for prevalent cases, incident cases, and total cohort, respectively.
[d] Number of days spent in long-term care facility.

Despite the fact that the use of antiviral medications was associated with significantly lower HZ-associated pain severity and duration, regardless of the phase of the HZ illness, only 52.3% were treated with antivirals at enrolment. This proportion is lower compared to that observed in Canada (88.9%), the USA (85.0%), Thailand (85.6%), and Spain (91.5%);[25,26,34,35] however this is probably due to the shorter time elapsed from symptom onset to enrolment in those studies compared to the current study. In support of this, antiviral medications were used in 95.6% of the incident cases included in our study.

A previous study showed that impaired immune status is associated with greater HZ severity of illness;[20] however we did not find a significant association, possibly due to the small number of immunocompromised patients in our study.

HZ-associated pain significantly interfered with all activities of daily living (ADL), particularly mood, enjoyment of life, general activities, and sleep; the highest level of interference was observed at baseline when the HZ-associated pain was maximal. The mean EQ-5D score, assessing patient mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, also paralleled the ADL impact of HZ, being lowest at baseline and increasing thereafter. In line with these findings, previous studies have also shown that acute HZ pain and discomfort has a significant negative impact on functional status and patient QoL.[34] In accordance with the severe burden of illness, significant HCRU was associated with the management of HZ, including visits to the primary care doctor, a specialist, or a physiotherapist, hospitalizations, and visits to the emergency department.

Several limitations of this study are worth noting. The study recruited prevalent cases who had already endured at least 7 days of illness since rash onset, which may have led to recall bias in the evaluation of their pain, QoL, and HCRU prior to or at rash onset. Furthermore, misclassification of disease cannot be ruled out, given the fact that laboratory confirmation of HZ infection was not required for the patient to be eligible for the study. Finally, our study included patients who sought care for HZ, which may have resulted in the inclusion of slightly more severe cases of HZ than those found in the general population. Moreover, prevalent cases may over-represent the group of patients requiring greater medical care compared to the general population.

In conclusion, the present study showed that HZ in South Korea is associated with significant morbidity and healthcare utilization and reduced quality of life. Patients older than 70 years of age are particularly at an increased risk of severe and long-lasting pain that often affects health-related quality of life and daily activities. In countries that have experienced rapid development and sustained economic growth, populations now have a better life expectancy and therefore the number of HZ and post-herpetic neuralgia cases is expected to increase in the coming years due to the steady increase in the elderly population. Such changes in the population demographics require modifications in the allocation of resources to reduce the burden of vaccine-preventable illnesses such as herpes zoster among those at the highest risk, namely patients ≥50 years of age.

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