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Predictors of postherpetic neuralgia in patients with herpes zoster: a pooled analysis of prospective cohort studies from North and Latin America and Asia

Kosuke Kawai [a,*], Emmanouil Rampakakis [b], Tsen-Fang Tsai [c], Hee Jin Cheong [d], Jittima Dhitavat [e], Alejandro Ortiz Covarrubias [f], Lin Yang [b], Miguel Cashat-Cruz [g], Homero Monsanto [h], Kelly Johnson [a], John S. Sampalis [b,i], Camilo J. Acosta [a]

[a] Global Health Outcomes, Merck & Co., Inc., 770 Sumneytown Pike, West Point, Pennsylvania, PA 19486, USA
[b] JSS Medical Research, St-Laurent, Quebec, Canada
[c] Department of Dermatology, National Taiwan University Hospital, Zhongzheng District, Taipei City, Taiwan
[d] Division of Infectious Diseases, Department of Internal Medicine, Korea University Guro Hospital, Seoul, South Korea
[e] Clinical Infectious Disease Research Unit, Department of Clinical Tropical Medicine, Faculty of Tropical Medicine, Mahidol University, Phutthamonthon District, Nakhon Pathom, Bangkok, Thailand
[f] Hospital Civil de Guadalajara Fray Antonio Alcalde, Guadalajara, Jalisco, Mexico
[g] Vaccines Latin America and the Caribbean, MSD Corp., Mexico City, DF, Mexico
[h] Latin America Health Outcomes Research, MSD (I.A.) Corp., Carolina, Puerto Rico
[i] McGill University, Montreal, Quebec, Canada

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SUMMARY

Objectives: The most common complication of herpes zoster (HZ) is postherpetic neuralgia (PHN), a persistent pain that can substantially affect quality of life (QoL). This analysis aimed to evaluate predictors of PHN in HZ patients.

Methods: A pooled analysis of prospective cohort studies of HZ patients aged ≥50 years from North America (Canada), Latin America (Brazil, Mexico, and Argentina), and Asia (Taiwan, South Korea, and Thailand) was performed. Patients within 14 days of rash onset were included. The incidence of PHN was defined as a worst pain score of ≥3, persisting/appearing at >90 days after rash onset. Socio-demographics, HZ disease characteristics, treatment, pain-related interference with activities of daily living, and health-related QoL were assessed.

Results: Of 702 patients with HZ, 148 (21.1%) developed PHN. Similar risks of PHN were observed across geographic regions. On multivariate analysis, older age, greater severity of pain at rash onset, employment status, walking problems at enrollment, and pain interference affecting social relationships were significantly associated with the development of PHN.

Conclusions: In addition to older age and severe acute pain, this study suggests that impaired physical and social functioning from acute zoster pain may play a role in the development of PHN in this prospective cohort study of HZ patients from North and Latin America and Asia.

1. Introduction

Herpes zoster (HZ) is caused by reactivation of the latent varicella zoster virus (VZV) in sensory ganglia and is typically characterized by painful, blistering rashes.[1] The lifetime risk of HZ is approximately 30%.[2] For some patients, pain continues to persist after the rash heals and develops into postherpetic neuralgia (PHN). PHN is the most common complication of HZ and occurs in approximately 5% to 30% of HZ patients.[3] The risk of PHN increases with age. PHN can persist for several months to several years, and even up to 10 years. PHN substantially affects patient quality of life (QoL) and can cause physical disability, emotional distress, and social isolation.[4] PHN patients experience different types of pain including a steady burning pain, intermittent stabbing or shooting pain, and stimulus-evoked pain (allodynia). Treatments for PHN include anticonvulsants, topical lidocaine or capsaicin, tricyclic

* Corresponding author. Tel.: +1 617 869 2513.
E-mail address: kkawai8@gmail.com (K. Kawai).

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antidepressants, and opioid analgesics.[4–6] However, each treatment has limited efficacy and patients are often refractory to these treatments. As an effective preventive strategy, a live-attenuated VZV vaccine (Zostavax by Merck) has been demonstrated to significantly reduce the risk of HZ and PHN.[7]

Understanding the predictors of PHN is important to enable healthcare professionals to identify patients at risk of PHN who might benefit from early treatment. It may also help researchers to better understand the pathophysiology of PHN. It is recognized that older age, greater acute pain severity, and greater rash severity increase the risk of developing PHN.[6,8–23] However, other factors, such as prodromal pain, female sex, and functional and psychosocial status, have rarely been evaluated or have not been consistently associated with the risk of PHN.[8,11,15] Conflicting results could be due to differences in the definition of PHN, study population, and methodology. Furthermore, prior research has been conducted mostly in North America and Europe, but less frequently in other geographic regions.

The objective of this study was to evaluate the predictors of PHN from a pooled analysis of prospective cohort studies of patients with HZ from North America (Canada), Latin America (Mexico, Brazil, and Argentina), and Asia (Taiwan, South Korea, and Thailand).

2. Methods

2.1. Study design and population

Data from the MASTER study (Monitoring and Assessing Shingles Through Education and Research), a prospective cohort study of patients with HZ conducted in seven countries (Canada, Brazil, Mexico, Argentina, Taiwan, South Korea, and Thailand) using the same methodology, were pooled.[20,24–28] Eligible participants were patients with a physician-confirmed diagnosis of HZ rash or zoster-associated pain with documented date of rash onset in the medical chart, ≥50 years of age, and capable of completing the study questionnaires. Patients were recruited at different time points during the course of their disease. However, the current analysis was restricted only to patients enrolled within 14 days of rash onset. Patients were followed prospectively for 6 months to assess their zoster-associated burden of illness, including severity and duration of pain, impact on health-related QoL, and healthcare utilization. All participants signed an informed consent form prior to any study-related procedure. The study was approved by local institutional review boards in each country.

2.2. Definition of postherpetic neuralgia

The incidence of PHN was defined as a worst pain score of ≥3, persisting or appearing more than 90 days after the onset of rash. A previous validation study has shown that worst pain scores of ≥3 occurring ≥90 days after rash onset significantly impair QoL and activities of daily living.[29] This definition was used in a clinical trial of zoster vaccination and other studies.[7]

2.3. Assessment

A physician reviewed the patient's characteristics of HZ and treatment at the time of recruitment. To assess zoster-associated pain and its impact on activities of daily living from the patient's perspective, the Zoster Brief Pain Inventory (ZBPI) and the Initial Zoster Impact Questionnaire (IZIQ) were used. The ZBPI is a validated self-administered questionnaire that assesses the severity of pain associated with HZ using a scale from 0 (no pain) to 10 (pain as bad as you can imagine).[29] The ZBPI also assesses the interference of pain with daily activities, including general activity, mood, walking ability, normal work, relations with other people, sleep, and enjoyment of life.

The following socio-demographics, characteristics of HZ, and health indicators were evaluated as potential predictors of PHN: age, sex, level of education, employment status, living alone, immune status, presence of other pain conditions, and pre-existing problems in the EQ-5D five health domains. The following HZ characteristics were also examined as predictors: severity of rash (number of lesions), worst pain score at rash onset, prodromal pain (duration and severity of pain), problems in EQ-5D health domains at rash onset, pain interference with daily activities at rash onset, and use of antiviral medications.

2.4. Statistical analysis

Baseline characteristics of HZ patients by PHN status were compared using the Chi-square test or Fisher's exact test, as appropriate, for categorical variables. To examine factors associated with the risk of developing PHN, binomial regression models were used with a log-link function and computed risk ratio (or relative risk, RR) and associated 95% confidence intervals (CI). The parsimonious multivariate regression model was built using a backward selection procedure. Variables with $p < 0.20$ in the univariate analysis were considered as candidates for the multivariate model, and variables with $p < 0.05$ were kept in the final model.

3. Results

A total of 702 patients with HZ were included in the analysis (Table 1). Approximately 38% of participants were aged 50–59 years, 31% were aged 60–69 years, and 31% were aged ≥70 years. The majority of patients were women (62%), and 32% reported being employed. The baseline clinical characteristics of HZ disease were generally comparable across the three geographic regions. About 58% of patients reported a severe worst pain score at rash onset (≥7). The majority of patients reported taking antiviral medications (87%).

Of 702 patients with HZ, 148 (21.1%) developed PHN. The age-specific risk of PHN ranged from 14.0% in adults 50–59 years of age and 20.6% in adults 60–69 years of age, to 29.7% in adults ≥70 years of age. In the univariate analysis, older age, employment status, greater severity of pain at rash onset, severe prodromal pain, problems in health domains in the EQ-5D at enrollment (except being anxious or depressed), and reported pain interference from acute HZ on activities of daily living (all seven items of ZBPI) were significantly associated with an increased risk of PHN (Table 2). No significant differences in the risk of PHN were found by geographic region, sex, level of education, living alone, immune status, presence of other pain conditions, pre-existing problems in the EQ-5D health domains, severity of rash, or use of antiviral medications during the acute phase.

In the multivariable regression model (Table 3), older age (60–69 vs. 50–59 years, RR 1.20, 95% CI 0.81–1.79; ≥70 vs. 50–59 years, RR 1.72, 95% CI 1.18–2.51), greater severity of pain at rash onset (moderate vs. no/mild, RR 2.46, 95% CI 0.91–6.66; severe vs. no/mild RR 3.58, 95% CI 1.36–9.45), employment status (RR 0.58, 95% CI 0.38–0.89), walking problems at enrollment (RR 1.47, 95% CI 1.11–1.93), and pain interference affecting relationships with other people (RR 1.69, 95% CI 1.27–2.25) were significantly associated with the development of PHN.

4. Discussion

The risk of developing PHN, defined as a pain score of ≥3 lasting or appearing more than 90 days after rash onset, was approximately

Table 1
Baseline characteristics

Characteristics	Asia (Taiwan, South Korea, Thailand) $n=339$	Latin America (Mexico, Brazil, Argentina) $n=132$	North America (Canada) $n=231$	Total $n=702$
Age, years, *n* (%)				
50–59	147 (43.4%)	33 (25.2%)	84 (36.4%)	264 (37.7%)
60–69	110 (32.4%)	44 (33.6%)	64 (27.7%)	218 (31.1%)
≥70	82 (24.2%)	54 (41.2%)	83 (35.9%)	219 (31.2%)
Sex, *n* (%)				
Female	205 (60.5%)	87 (66.4%)	140 (60.6%)	432 (61.6%)
Male	134 (39.5%)	44 (33.6%)	91 (39.4%)	269 (38.4%)
Level of education, *n* (%)				
Primary/grade school	128 (38.6%)	63 (48.1%)	32 (14.0%)	223 (32.3%)
High school	120 (36.1%)	27 (20.6%)	94 (41.2%)	241 (34.9%)
College or university	84 (25.3%)	41 (31.3%)	102 (44.7%)	227 (32.8%)
Employed, *n* (%)	111 (32.7%)	43 (32.8%)	71 (31.0%)	225 (32.2%)
Living alone, *n* (%)	30 (8.8%)	36 (27.5%)	71 (33.0%)	137 (20.0%)
Presence of other pain condition, *n* (%)	96 (28.3%)	48 (36.6%)	114 (49.4%)	258 (36.8%)
Impaired immune status, *n* (%)	36 (10.6%)	21 (15.9%)	9 (3.9%)	66 (9.4%)
Herpes zoster characteristics				
Primary dermatome region, *n* (%)				
Thoracic	152 (45.0%)	53 (41.7%)	109 (49.3%)	314 (45.8%)
Trigeminal nerve	65 (19.2%)	10 (7.9%)	12 (5.4%)	87 (12.7%)
Cervical	67 (19.8%)	36 (28.3%)	42 (19.0%)	145 (21.1%)
Lumbar	39 (11.5%)	19 (15.0%)	43 (19.5%)	101 (14.7%)
Sacral	15 (4.4%)	9 (7.1%)	15 (6.8%)	39 (5.7%)
Severity of rash (number of lesions), *n* (%)				
None or <20 (mild)	129 (38.1%)	84 (63.6%)	141 (61.3%)	354 (50.5%)
21–50 (moderate)	117 (34.5%)	28 (21.2%)	49 (21.3%)	194 (27.7%)
≥50 (severe)	93 (27.4%)	20 (15.2%)	40 (17.4%)	153 (21.8%)
Worst pain score at rash onset, *n* (%)				
No/mild (0–2)	36 (10.7%)	9 (6.9%)	26 (11.5%)	71 (10.2%)
Moderate (3–6)	124 (36.8%)	21 (16.2%)	74 (32.6%)	219 (31.6%)
Severe (≥7)	177 (52.5%)	100 (76.9%)	127 (55.9%)	404 (58.2%)
Presence of prodromal pain, *n* (%)	227 (67.0%)	88 (67.2%)	175 (76.8%)	490 (70.2%)
Antiviral medications, *n* (%)				
Aciclovir, valaciclovir, famciclovir	282 (83.2%)	118 (89.4%)	212 (91.8%)	612 (87.2%)
Did not receive	57 (16.8%)	14 (10.6%)	19 (8.2%)	90 (12.8%)

21% in this prospective cohort study of patients with HZ from North and Latin America and Asia. Older age, greater severity of pain at rash onset, employment status, walking problems at enrollment, and pain interference affecting relationships with other people, were identified as independent predictors of PHN.

Approximately 21% of patients aged ≥50 years developed PHN, with the risk increasing with older age. The risk of PHN was almost 30% among patients aged ≥70 years. A number of prospective cohort studies across countries have also noted a high risk of PHN, ranging from approximately 10% to ≥30%, in elderly patients with HZ.[2,3,21,30] A population-based, retrospective cohort study in the USA found that the risk of PHN (defined as at least 90 days of documented pain) was 10% in adults 60–69 years of age, 17% in adults 70–79 years of age, and 20% in adults ≥80 years of age.[2] The generally higher estimate in the current analysis could be explained by the fact that patients were followed prospectively thus allowing a more accurate assessment of pain, or by differences in the populations included. It is also possible that patients with severe cases of HZ were more likely to have participated in the present study.

It is well-recognized that a greater severity of acute pain at rash onset is a risk factor for PHN (Table 4).[8–23] Those who suffered from severe pain most likely had a severe infection, resulting in substantial neural damage. Consistent with prior studies, the present study confirmed that the severity of acute pain is a risk factor for PHN. Biological and psychosocial factors are important in understanding the pathophysiology of chronic pain.[16,31] Thus, an evaluation was done to determine whether pain-related interference with diverse activities of daily living and living alone are associated with an increased risk of the development of PHN. It was found that walking problems at enrollment and HZ pain interference affecting relationships with other people remained significant predictors of PHN in the multivariate analysis. It was also found that working adults, who are most likely healthy and active, were less likely to develop PHN. Although few studies have evaluated such factors, they have also suggested that impaired physical and social functioning may play a role in the development of PHN.[16,20,23,32] Patients with predisposing vulnerabilities, possibly with a reduced threshold of nociception as a result of genetic factors or prior stressful life events, are more likely to be vulnerable and suffer greatly from severe infection and develop PHN.[31]

Dworkin et al. and several other investigators have found that a greater severity of rash is a risk factor for PHN.[9,13,15,18,19] However, the present study did not confirm this association. Prospective cohort studies with participants recruited from real-world community settings (as opposed to participants in clinical trials) have also shown the severity of rash not to be a risk factor for PHN.[14,17,23] It is possible that due to the wide recruitment window in the present study (up to 14 days since rash onset), the rash in some patients may have alleviated, which may have limited our ability to observe such an association.

Other possible predictors of PHN were also evaluated. Several studies have suggested that a severe or longer duration of prodromal pain may increase the risk of developing PHN.[8,11,15] In the present study, the presence of severe prodromal pain was associated with an increased risk of PHN in the univariate analysis, but it did not remain significant after adjusting for severity of acute pain and other factors in the multivariate analysis. Although a few studies have suggested that female sex may be a risk factor, the majority of prior studies and the present study found no difference

Table 2
Univariate analysis: predictors of postherpetic neuralgia among patients with herpes zoster

Predictors	Developed PHN, *n* (%)	Crude RR	95% CI	*p*-Value
Region				
Taiwan, South Korea, and Thailand	66 (19.5%)	0.80	(0.59, 1.10)	0.17
Mexico, Brazil, and Argentina	26 (19.7%)	0.81	(0.54, 1.23)	0.32
Canada	56 (24.2%)	Reference		
Age, years				
50–59	37 (14.0%)	Reference		
60–69	45 (20.6%)	1.47	(0.99, 2.19)	0.055
≥70	65 (29.7%)	2.12	(1.48, 3.04)	<0.001
Sex				
Male	55 (20.4%)	Reference		
Female	93 (21.5%)	1.05	(0.78, 1.42)	0.73
Level of education				
Primary/grade school	52 (23.3%)	Reference		
High school	51 (21.2%)	0.79	(0.55, 1.14)	0.21
College or university	42 (18.5%)	0.91	(0.65, 1.28)	0.58
Employment status				
Yes	27 (12.0%)	0.47	(0.32, 0.69)	<0.001
No	121 (25.5%)	Reference		
Living alone				
Yes	35 (25.5%)	1.32	(0.95, 1.84)	0.10
No	106 (19.3%)	Reference		
Health conditions				
Immune status				
Impaired	13 (19.7%)	0.93	(0.56, 1.55)	0.77
Normal	135 (21.2%)	Reference		
Presence of other pain condition				
Yes	56 (21.7%)	1.05	(0.78, 1.40)	0.77
No	92 (20.8%)	Reference		
Pre-existing problems in EQ-5D health domains before HZ (no problem as reference)				
Walking	23 (26.4%)	1.29	(0.88, 1.90)	0.19
Self-care	9 (25.0%)	1.19	(0.66, 2.14)	0.56
Usual activities	17 (23.0%)	1.10	(0.71 1.72)	0.68
Having pain or discomfort	49 (23.8%)	1.18	(0.88, 1.60)	0.27
Being anxious or depressed	28 (17.7%)	0.80	(0.55, 1.16)	0.23
Herpes zoster characteristics				
Severity of rash (number of lesions)				
<20 (no/mild)	65 (18.4%)	Reference		
21–50 (moderate)	47 (24.2%)	1.32	(0.95, 1.84)	0.10
≥50 (severe)	36 (23.5%)	1.28	(0.89, 1.84)	0.18
Worst pain score at rash onset				
No/mild (0–2)	4 (5.6%)	Reference		
Moderate (3–6)	33 (15.1%)	2.68	(0.98, 7.29)	0.054
Severe (≥7)	109 (27.0%)	4.79	(1.82, 12.58)	0.001
Duration of prodromal pain				
None	38 (18.3%)	Reference		
1–2 days	25 (17.5%)	0.96	(0.61, 1.51)	0.85
3–4 days	41 (24.3%)	1.33	(0.90, 1.97)	0.16
≥5 days	40 (23.3%)	1.27	(0.86, 1.89)	0.23
Worst pain score for prodromal pain				
No/mild (0–2)	39 (15.5%)	Reference		
Moderate (3–6)	39 (20.4%)	1.32	(0.88, 1.97)	0.18
Severe (≥7)	67 (27.1%)	1.75	(1.23, 2.50)	0.002
Problems in EQ-5D health domains at enrollment (no problem as reference)				
Walking	62 (31.8%)	1.87	(1.41, 2.48)	<0.001
Self-care	42 (32.8%)	1.77	(1.31, 2.39)	<0.001
Usual activities	80 (27.8%)	1.69	(1.27, 2.25)	<0.001
Having pain or discomfort	130 (23.4%)	1.91	(1.20, 3.06)	0.007
Being anxious or depressed	82 (23.6%)	1.27	(0.95, 1.69)	0.11
Pain interference at enrollment, reported ≥5 (<5 as reference)				
General activity	91 (27.7%)	1.83	(1.36, 2.47)	<0.001
Mood	86 (26.1%)	1.59	(1.18, 2.12)	0.002
Walking ability	50 (31.3%)	1.73	(1.29, 2.32)	<0.001
Normal work	77 (27.4%)	1.64	(1.23, 2.19)	0.001
Relations with other people	65 (31.9%)	1.94	(1.46, 2.57)	<0.001
Sleep	94 (26.0%)	1.65	(1.22, 2.23)	0.001
Enjoyment of life	85 (26.0%)	1.56	(1.17, 2.09)	0.003
Antiviral medications				
Aciclovir, valaciclovir, famciclovir	133 (21.7%)	1.30	(0.80, 2.12)	0.28
Did not receive	15 (16.7%)	Reference		
Timely antiviral medications				
Received within 72 h of rash onset	70 (18.6%)	1.61	(0.97, 2.67)	0.067
Received after 72 h of rash onset	63 (26.8%)	1.11	(0.67, 1.85)	0.68
Did not receive	15 (16.7%)	Reference		

PHN, postherpetic neuralgia; RR, relative risk; CI, confidence interval; HZ, herpes zoster.

Table 3
Multivariate analysis: predictors of postherpetic neuralgia among patients with herpes zoster

Predictors	Adjusted RR	95% CI	*p*-Value
Age, years			
50–59	Reference		
60–69	1.20	(0.81, 1.79)	0.36
≥70	1.72	(1.18, 2.51)	0.005
Employment status			
Yes	0.58	(0.38, 0.89)	0.012
No	Reference		
Worst pain score at rash onset			
No/mild (0–2)	Reference		
Moderate (3–6)	2.46	(0.91, 6.66)	0.077
Severe (≥7)	3.58	(1.36, 9.45)	0.01
Walking problems at enrollment			
Yes	1.47	(1.11, 1.93)	0.006
No	Reference		
Pain interference at enrollment, relations with other people			
Yes	1.69	(1.27, 2.25)	<0.001
No	Reference		

RR, relative risk; CI, confidence interval.

in the risk of PHN between women and men. Antiviral therapy is important to reduce the replication of the virus and the severity and duration of pain during the acute phase. However, consistent with a recent review, timely antiviral medication was not associated with the incidence of PHN in the present study.[33]

Several limitations of this study are worth noting. Patients who participated may not comprise a random sample of patients from the general population, possibly limiting the generalizability of the results. The type of pain was not characterized, which may have allowed a better understanding of the pathophysiology of PHN. Patients suffering from PHN experience different types of pain, presumably because of different pathophysiological mechanisms involving sensitization in the peripheral and central nervous system, deafferentation, and possibly chronic inflammation.[5,6]

This study has several strengths. The findings are based on a methodologically robust, prospective cohort study using the same questionnaires across countries. Prior research has rarely been conducted in Latin America and Asia; thus, a multi-country study including those regions was conducted. Multiple different definitions of PHN have been used previously. However, the validated definition of PHN, which is a pain score of ≥3 (clinically meaningful pain) lasting or appearing more than 90 days after rash onset, was used in the present research.

In conclusion, the risk of developing PHN was over 20% in this prospective cohort study of patients with HZ from North and Latin America and Asia. It is confirmed that older age and a greater severity of pain at rash onset are risk factors for PHN. Additionally, this study suggests that impaired physical and social functioning from acute pain of HZ may also be risk factors for PHN. HZ patients who are at greater risk of developing PHN should be monitored closely for early treatment. Early prevention through vaccination should be considered to reduce the risk of developing HZ and PHN.

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Ethical approval: Approval for this post-hoc analysis of available data was not required.

Conflict of interest: KK was a consultant for Merck & Co., Inc. ER, LY, and JSS are employees of JSS Medical Research, the contract Research Organization responsible for the management of the MASTER studies and data analysis. TFT has performed clinical trials and has received speaking fees from MSD. HJC and JD have no conflicts of interest. AOC has received payments to speak from Merck Sharp & Dohme, Abbott Laboratories, Bayer Health Care, and Sanofi Laboratories. HM is an employee of Merck (Latin America Health Outcomes Research Ugad). KJ is a post-doctoral research fellow at Temple University funded by Merck & Co., Inc. MCC is an employee of Merck and Co., Inc. CJA is an employee of Merck Global Health Outcomes – Vaccines.

Table 4
Prior studies examining predictors of postherpetic neuralgia (PHN)

References	PHN definition	Risk of PHN	Predictors of PHN
Whitley et al.[8]	Prolonged HZ-associated pain	NA (*n* = 2367)	Age, severity of acute pain, and presence of prodromal pain
Dworkin et al.[9]; Nagasako et al.[10]	Pain persisting for ≥30 or ≥90 days	30% (*n* = 419)	Age, severity of acute pain, severity of rash, and antiviral treatment
Decroix et al.[11]	Prolonged HZ-associated pain	NA (*n* = 1897)	Age, severity of acute pain, intensity of prodromal pain, HZ ophthalmicus
Haanpaa et al.[12]	Pain persisting for ≥90 days	25% (28/113)	Age, severity of acute pain, and allodynia
Kurokawa et al.[13]	Pain persisting for ≥90 days	NA (*n* = 263)	Age, severity of rash, disturbed sleep, and hypaesthesia
Scott et al.[14]	Pain persisting for ≥90 days	27% (42/153)	Age and severity of acute pain
Jung et al.[15]	Pain persisting for ≥120 days	12% (114/965)	Age, female sex, severity of acute pain, severity of rash, and presence of prodromal pain
Katz et al.[16]	Pain persisting for ≥120 days	20% (20/102)	Age, severity of acute pain, and psychosocial factors
Coen et al.[17]	Pain score ≥3 persisting for ≥90 or ≥180 days	9.6% (24/250)	Age and severity of acute pain
Opstelten et al.[18]	Pain score ≥3 persisting for ≥90 days	8% (46/598)	Age, severity of acute pain, severity of rash, and duration of rash before consultation
Volpi et al.[19]	Pain score ≥3 persisting for ≥180 days	32% (70/219)	Age, severity of acute pain, severity of rash, and longer duration of prodromal pain
Drolet et al.[20]	Pain score ≥3 persisting for ≥90 days	22.5% (56/249)	Age, severity of acute pain, and limitation in performing usual activities
Parruti et al.[21]	Pain persisting for ≥30 or ≥90 days	30% (130/441)	Age, severity of acute pain, smoking, trauma, and missed antiviral prescription
Kanbayashi et al.[22]	Pain persisting for ≥90 days	52% (38/73)	Age and deep pain
Bouhassira et al.[23]	Pain persisting for ≥90 days	11.6% (127/1091)	Age, male sex, neuropathic quality of pain, interference of pain on daily activities, and physical component summary score

NA, not available.

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