ORIGINAL ARTICLE

Pain, Itch, Quality of Life, and Costs after Herpes Zoster

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■ **Abstract**

Background: Herpes zoster (HZ) and postherpetic neuralgia are known to have a profound effect on the patient's quality of life, but the incidence and severity of itch and its relation with pain and quality of life in the long term are still relatively unknown.

Objective: The aim of this study was to measure the presence and severity of pain and itch and impact on quality of life in patients over 50 years old with HZ.

Methods: We enrolled 661 patients with HZ in this 12-month observational study. Patient data were collected via a web-based questionnaire. Outcomes were pain, itch, burden of illness, impact on patient's daily life, impact on quality of life, and healthcare costs.

Results: At inclusion, 94% of patients reported any pain, 74.3% significant pain, and 26% severe pain. After 3 months, 18.8% of patients suffered from postherpetic neuralgia. At inclusion, 70.8% of patients had any itch, 39.2% significant itch, and 7.3% severe itch. The occurrence of pain increases costs and has a high impact on the quality of life, lowering EQ-5D scores by an average of 18%. In contrast, itch has little effect on the quality of life.

Conclusions: Pain and itch are highly prevalent months after HZ. Pain caused by HZ has a large impact on quality of life, burden of illness, impact on daily life, and health care costs for these patients. The impact of itch on quality of life is relatively small. ■

Key Words: herpes zoster, postherpetic neuralgia, pain, itch, quality of life

INTRODUCTION

Herpes zoster (HZ) is a common disease with an estimated lifetime prevalence between 20% and 30% t.[1–3] The incidence across all age groups is between 2.0 and 4.6 cases per 1,000 persons per year, but rises rapidly after the age of 50 years, with an incidence of 9.1 cases per 1,000 persons per year in the age group < 75 years.[4–7] The overall incidence is expected to rise in the near future because of the aging population.[8]

If necessary, HZ is usually treated with analgesics.[9,10] Antiviral drugs can relieve pain and accelerate rash healing in some patients, but have no effect on the incidence of postherpetic neuralgia (PHN).[1,11] Treatment with opiates, anti-epileptics, tricyclic antidepressants, and capsaicin is possible in patients with insufficient relief of symptoms after using paracetamol and NSAIDs.[9] Vaccines for chickenpox and herpes zoster have been developed in the last 20 years, and these have been included in vaccination programs in multiple countries.[12]

The most common complication of HZ is PHN caused by sustained peripheral nerve damage during the HZ episode.[10] PHN is usually defined as any or clinically significant zoster-related pain which is present 1 to 6 months after the onset of rash.[10] PHN occurs, depending on the chosen definition, in approximately

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7% to 22% of all patients with HZ and can last multiple years.[13–15] Known risk factors for PHN include older age, ophthalmic involvement, and greater severity of pain, rash, and prodrome during the beginning of the HZ episode.[15–17] The incidence is also increased among individuals with chronic diseases as well as immune-compromised patients.[10,16]

Herpes zoster and PHN are known to have a profound effect on the patient's ability to perform their daily tasks and quality of life.[18] The incidence and severity of itch and its relation with pain and quality of life in the long term are still relatively unknown. The aim of this study was to measure the presence and severity of both pain and itch and their impact on quality of life in patients over 50 years old with acute HZ.

METHODS

Study Design

For this observational study, patients were recruited by 300 participating general practitioners (GP). Also, we advertised in the Google search engine at the keywords "herpes zoster" and "shingles". The advertisement linked to the study website where patients could register for the study. Diagnosis was established by clinical evaluation by the GP. Patients filled out web-based questionnaires at inclusion and after 2 weeks and 1, 3, 6, 9, and 12 months. Patients unable to fill out the web-based questionnaire were asked to answer the questionnaires by telephone.

Patients

Inclusion criteria were age over 50 years, ability to speak Dutch, and presence of acute HZ with confirmation of diagnosis by their GP within 7 days after onset of rash. All participants provided written informed consent. Patients with HZ were treated according to normal clinical practice. Baseline data were collected through the GP and the patient inclusion form, which included gender, age, severity of rash, and medical history.

Measurements

The questionnaires at all 7 time points included visual analog scale (VAS) scores for pain and itch, medication use, description of pain, Short Form 12 health survey (SF-12), Euroqol EQ-5D, and Zoster Brief Pain Inventory (ZBPI).[19–21] The healthcare cost questionnaire TIC-P was filled out at inclusion and 3, 6, 9, and 12 months.[22] This questionnaire measures the number of contacts with healthcare providers, including the GP, medical specialists, paramedics, hospital admissions, medication, and out-of-pocket costs.

Pain and itch were considered absent at scores below 0.5 cm on a 10-cm VAS, significant pain and itch were defined as $\geq$ 3 cm on a 10-cm VAS, and severe pain and itch were defined as $\geq$ 7 cm on a 10-cm VAS. Postherpetic neuralgia and itch were defined as any zoster-related pain or itch which was present 3 months after the onset of rash. The scores from the SF-12, EQ-5D, ZBPI, and TIC-P were calculated in accordance with the authors' recommendations.[19–22] Normative data for calculating physical and mental component summaries of the SF-12 in the Dutch population were extracted from the research paper by Mols et al.[23]

Statistical Analyses

Descriptive statistical analyses were performed using SPSS (version 21.0). If data had a normal distribution, mean and 95% confidence interval were calculated; otherwise, median and IQR were reported. Box plots were created according to Tukey's method.[24] Missing data were imputed for pain VAS, itch VAS, and the 5 separate questions of the EQ-5D at all 7 time points. A total of 279 patients had values missing for 1 or more of these variables. The average percentage of missing data per variable was 15.8%. Data for these variables are reported using pooled results from 20 imputations with 100 iterations per imputation using Predictive Mean Matching in R (version 3.1.1) and the MICE package (version 2.22).

RESULTS

Patients

We identified 926 patients potentially suffering from HZ, of which 661 patients were enrolled in the study (Figure 1). Of the enrolled patients, 419 were included by their GP and 242 enrolled through the study website. Loss to follow-up was 8.2% at 6 months and 19.5% at 12 months. Baseline characteristics are shown in Table 1.

Occurrence of Pain and Itch

Of all patients, 94% reported pain at inclusion, 74.3% had significant pain, and 26.0% had severe pain

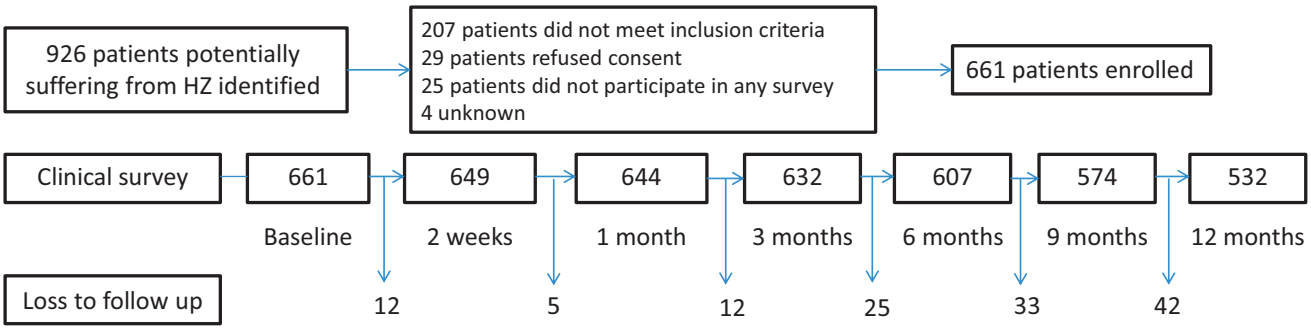

Figure 1. Inclusion and loss to follow up.

Table 1. Patient Demographics and Baseline Clinical Characteristics

	Age Groups			
	50 to 59 years	60 to 69 years	≥ 70 years	All
Patient demographics				
Patients, *n* (%)	232 (35.1)	245 (37.1)	184 (27.8)	661 (100)
Male sex, *n* (%)	73 (31.6)	111 (45.5)	69 (37.5)	254 (38.4)
Age, median, year	55	64	75	63
Clinical characteristics at inclusion				
Pain, median, cm VAS	4.75	5.1	5.6	5.1
Itch, median, cm VAS	2.55	2.1	0.75	2.1
EQ-5D, median	0.78	0.81	0.81	0.81
Level of health, median, cm VAS	6.1	6.1	6.1	6.1
Use of medication for HZ, *n* (%)	142 (61.2)	167 (68.2)	144 (78.3)	453 (68.5)
Affected skin area at inclusion, *n* (%)				
Cranial	8 (3.4)	9 (3.7)	11 (6)	28 (4.2)
Cervical	43 (18.5)	50 (20.4)	37 (20.1)	130 (19.7)
Thoracic	134 (57.8)	145 (59.2)	101 (54.9)	380 (57.5)
Lumbar	42 (18.1)	35 (14.3)	24 (13)	101 (15.3)
Sacral	5 (2.2)	6 (2.4)	11 (6)	22 (3.3)
Amount of vesicles at inclusion, *n* (%)				
20 or less	156 (67.2)	140 (57.3)	107 (58.2)	403 (61)
21 to 46	56 (24.1)	72 (29.2)	52 (28.3)	180 (27.2)
47 or more	20 (8.6)	33 (13.6)	25 (13.6)	78 (11.8)

VAS, visual analog scale.

(Figure 2). At 3 months, these percentages were 18.8%, 6.5%, and 0.8%, respectively. After 1 year, 7.6% still had any pain, 3.1% had significant pain, and 0.2% severe pain. The percentages for itch at inclusion were 70.8% for all itch, 39.2% for significant itch, and 7.3% for severe itch (Figure 3). At 1 month, these percentages were 29.8%, 8.2% and 1.1%, and at 1 year, they were 10.5%, 3.5%, and 0.2%, respectively. The median duration of both pain and itch was 3 weeks and 1 week for significant pain.

At inclusion, 67% of the patients had both pain and itch, while 26.6% had only pain and 3.5% had only itch (Figure 4A). The percentages of all patients with pain and itch and only pain declined rapidly after inclusion, with the percentage of patients with only itch rising and then remaining stable for multiple months. After 3 months, the distribution of patients suffering from only pain, only itch, and both pain and itch was 1:1:1 (Figure 4B). After 12 months, itch was more prevalent than pain or the combination of pain and itch (Figure 4C).

Quality of Life, Burden of Illness, and Impact on Daily Life

The occurrence of pain had a high impact on the quality of life of patients suffering from HZ. The occurrence and severity of itch had little effect on the quality of life. The figures of EQ-5D, SF-12, and ZBPI (Figure 5) showed similar results. Greater pain severity resulted in lower EQ-5D scores, but even pain considered non-significant (VAS 0.5 to 2.9) was found to have a significant effect on quality of life (Figure 6).

Medication Use

Thirty-eight percent of patients were prescribed antiviral medication at diagnosis, 24.5% were given paracetamol, and 13.2% a NSAID. Opiates, topical medication, and lidocaïne were each prescribed in 5% to 10% of patients. The amount of patients using medication at 3, 6, and 12 months was 8.9%, 4.3%, and 3.4%, respectively.

Subgroup Analysis

Affected Skin Area and Types of Pain. No differences in pain and itch severity or occurrence were found for

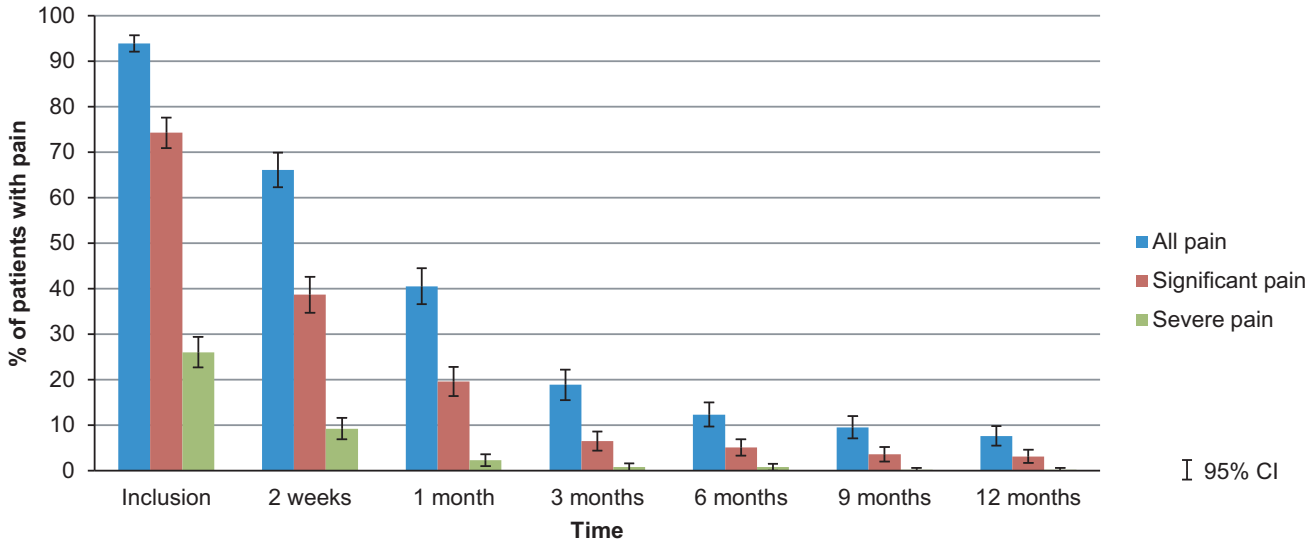

Figure 2. Percentage of patients with pain over time.

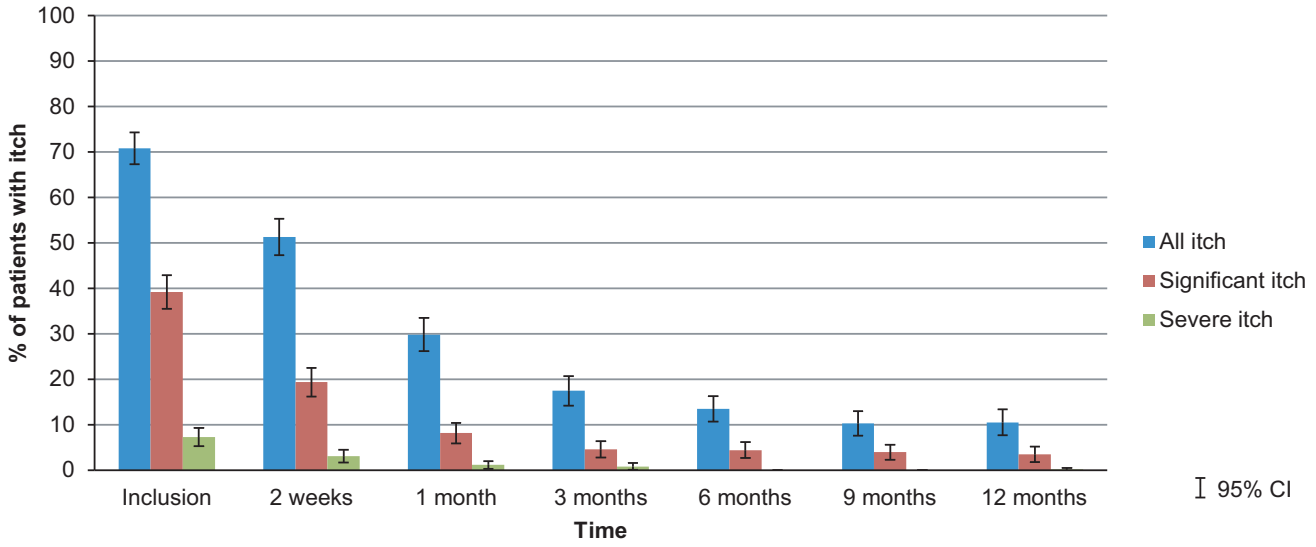

Figure 3. Percentage of patients with itch over time.

the different affected skin areas and types of pain (stabbing, nagging, burning, electrical, and throbbing).

Amount of Vesicles. Patients with more vesicles had a higher chance of experiencing pain. This observed effect remained consistent during the entire follow-up period of 12 months—long after the vesicles had disappeared. The amount of vesicles was not related to itch at any of the time points.

Analyses by Age Group. No significant differences were found in the occurrence of pain and itch between the age groups of 50 to 60, 60 to 70, and 70 years and older (Figure 7). Median VAS scores for itch and pain in patients with either symptom were found to remain at a higher level for a longer time in the age group above 70 years (Figure 8). EQ-5D scores for the age group above 70 years were lower than in the other age groups at baseline, but showed a similar trend when compared to the other age groups across all 7 time points. No other clinically and statistically significant differences were found between the age groups for the other outcomes.

Healthcare Consumption and Costs. Sixty percent of patients visited their GP only once in the first 6 months after diagnosis. Twenty percent and 10% of patients

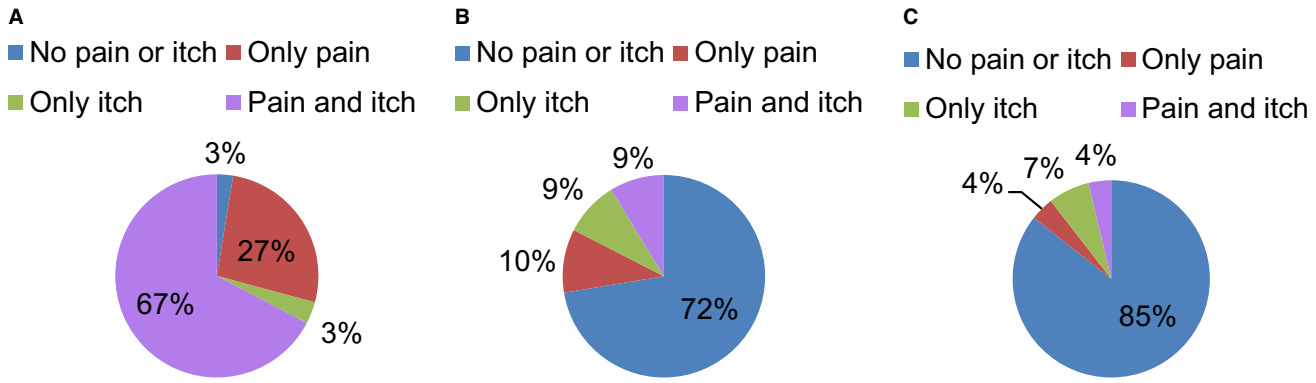

Figure 4. Distribution of patients with itch or pain at inclusion. (A) Distribution of patients with itch or pain at inclusion. (B) Distribution of patients with itch or pain after 3 months. (C) Distribution of patients with itch or pain after 12 months.

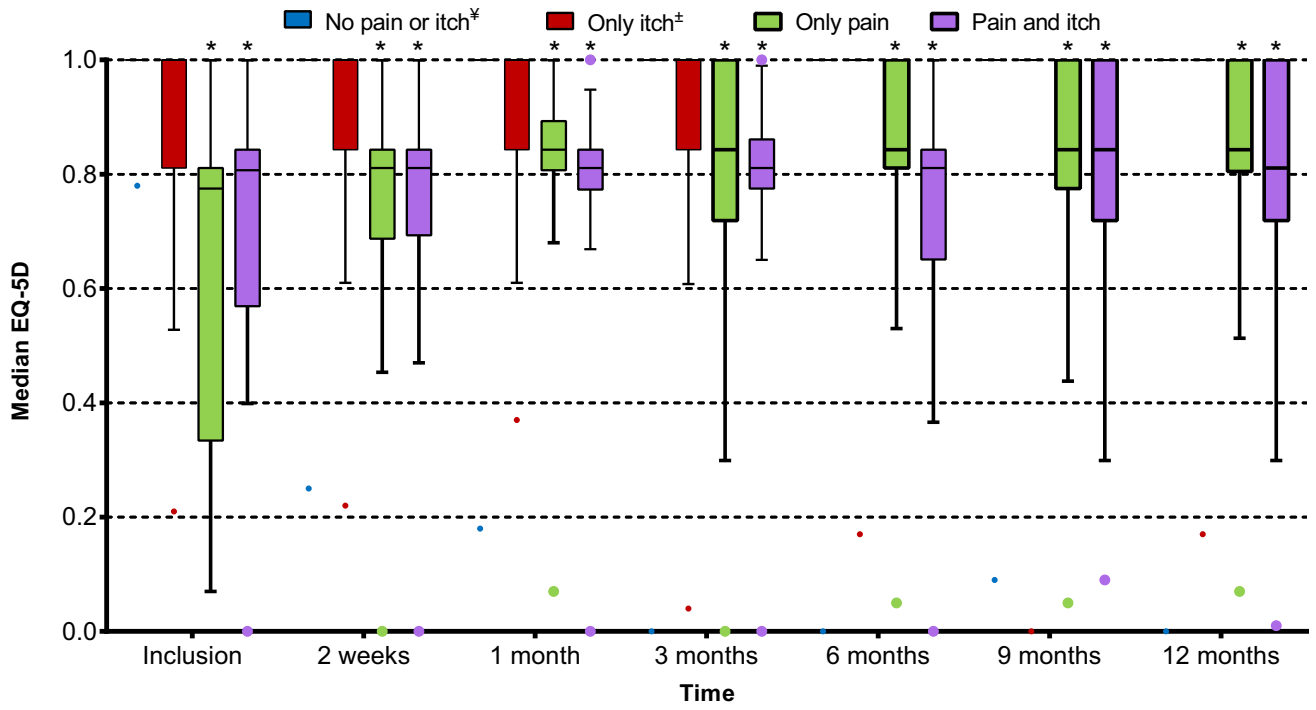

Figure 5. Median EQ-5D over time.

visited their GP 2 or 3 times, respectively, and 9% had between 4 and 7 consultations. Median direct and indirect healthcare costs and loss of production costs were between 100 and 175 euros per 3 months for the significant pain group and between 25 and 60 euros per 3 months in the group without pain (Figure 9).

DISCUSSION

After HZ, pain and itch are the most burdensome symptoms and often occur together. Itch is shown to be even more persistent over time than pain. However, pain has a higher impact on quality of life. The commonly heard statement that itch is worse than pain is not supported by our data.

The results from the present study show that 50% of patients suffering from HZ are pain-free at 3 weeks and itch-free at 1 week. However, almost 1 in 5 patients still have pain 3 months after the initial rash and are suffering from PHN from that moment on. Pain was found to have a profound effect on the quality of life as measured by the EQ-5D, SF-12, and

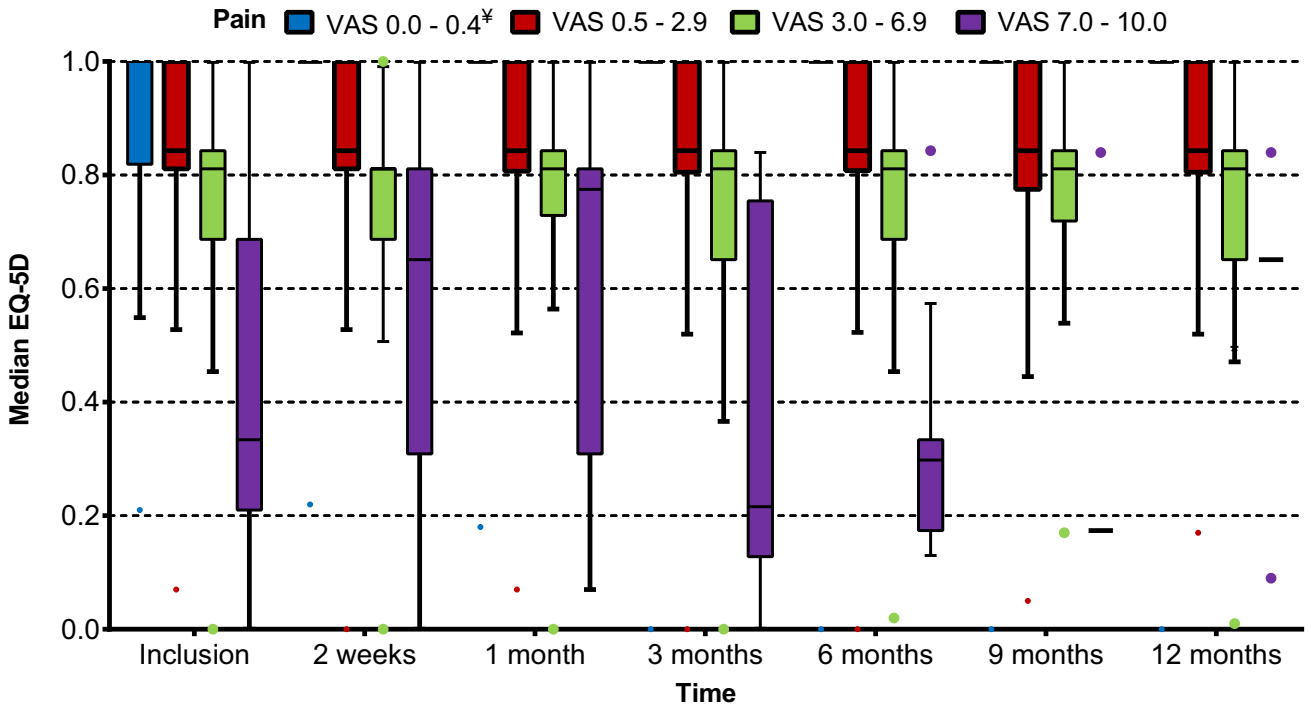

Figure 6. Median EQ-5D over time.

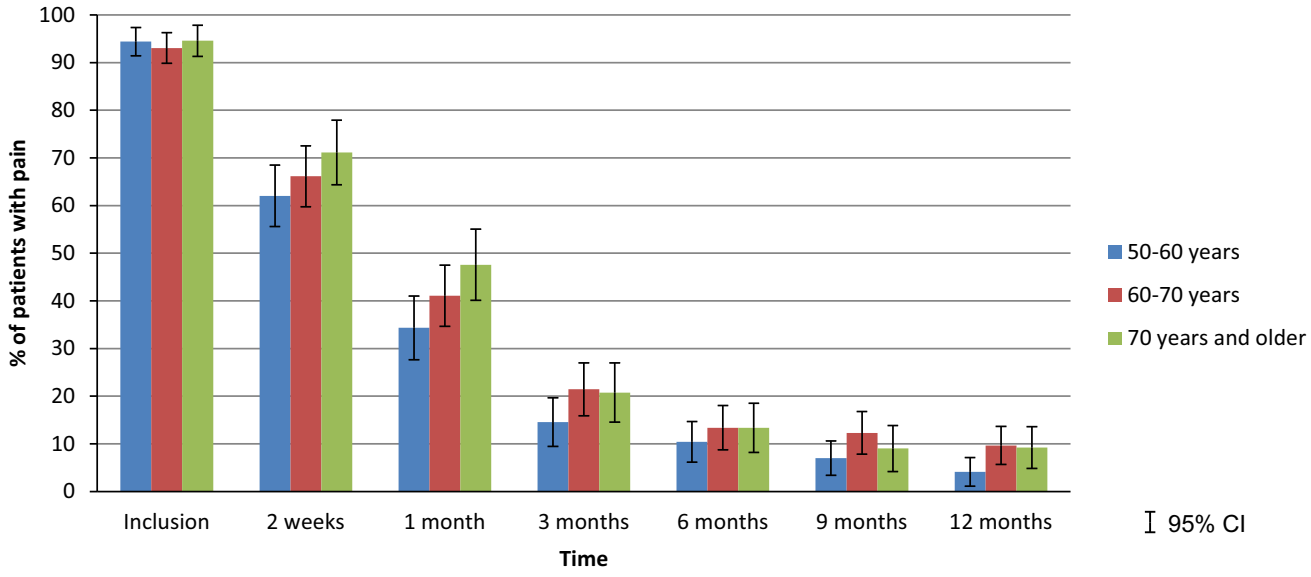

Figure 7. Percentage of patients with pain over time.

ZBPI-I. We were surprised by the finding that the severity of pain does not influence the quality of life in a significant matter after 1 month and that the occurrence of itch has little to no effect on the quality of life. Itch was nonetheless found to be a more persistent symptom than pain. Although there is still no effective treatment for the underlying disease, most patients perceive a large reduction in severity of symptoms by more than 50% after using various antivirals and pain medication. We found that HZ and PHN lead to an increase in direct and indirect healthcare costs.

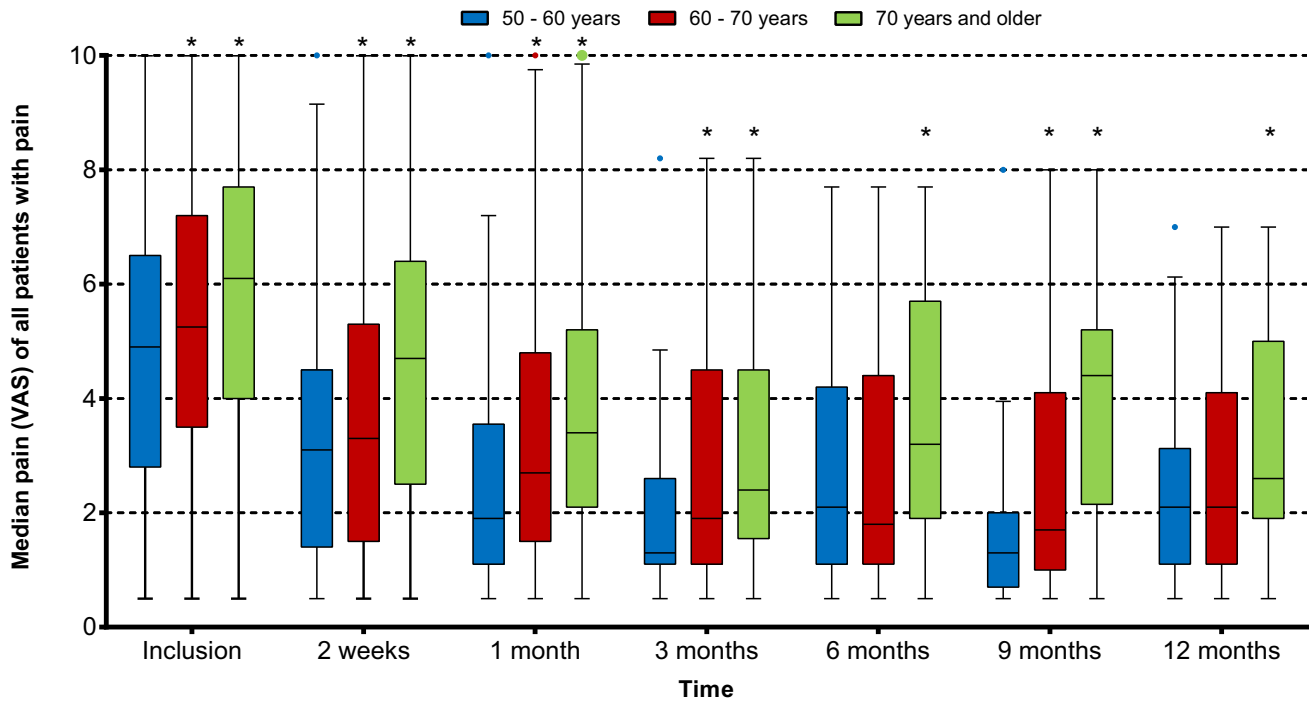

Figure 8. Median pain (VAS) of all patients with pain over time.

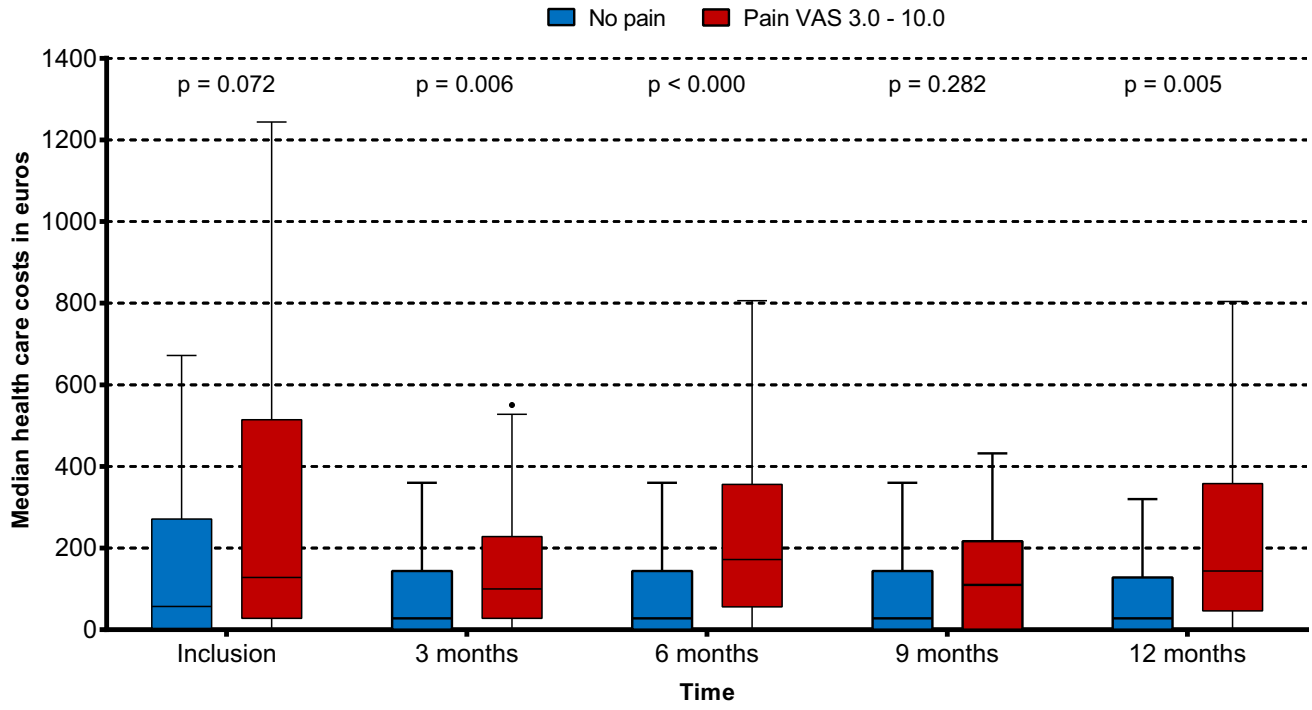

Figure 9. Median direct and indirect health care costs per 3 months over time.

To our knowledge, this is the first study to assess the long-time occurrence and severity of itch and its effect on quality of life in all patients older than 50 years with HZ. In an earlier study from a combined cohort from 3 centers with 177 patients with HZ and 409 with PHN, an incidence was found of 34% for patients with HZ

and 43% in PHN patients.[25] In the present study, a higher incidence was found for patients with HZ (70%).

Our findings related to occurrence and severity of pain and impact on quality of life are similar to the findings of other studies.[14,18,26–33] Contrary to Oxman et al.,[14] we found that mild pain (VAS < 3 cm) did, in fact, influence quality of life. This finding has influence on the definition of PHN. It is justified to consider all pain, even at low intensity, to be included in the definition of PHN.

The unexpectedly low impact of itch on quality of life may be influenced by the choice for generic questionnaires to measure quality of life. The EADV PruNet initiative recently recommended the ItchyQoL as the primary measuring tool for quality of life in chronic pruritus.[34] However, this questionnaire is not able to compare different symptoms. In the present study, findings in the EQ-5D, SF12, and ZBPI-I questionnaires were consistent and allowed a comparison between the effect of pain and itch on quality of life.

Strengths of our study include the prospective design and the considerable number of participants. Web-based data acquisition proved to be possible in this population of patients above 50 years of age. However, loss to follow-up exceeded 10% after 6 months and reached 19.5% at 12 months. We compensated for this loss to follow-up and other missing values by imputing the missing data.

CONCLUSION

Pain and itch are prevalent months after an initial HZ episode in large numbers of patients above 50 years of age with almost 19% of patients suffering from postherpetic neuralgia and 18% suffering from postherpetic itch. Pain caused by HZ has a large impact on quality of life, burden of illness, impact on daily life, medication use, and healthcare costs for these patients. The impact of itch on quality of life is relatively small.

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AUTHOR CONTRIBUTIONS

AvW designed the study and acted as principal investigator. YA performed the data analysis and wrote the first draft. Both authors contributed to further drafts and approved the final manuscript.

DISCLOSURES

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REFERENCES

1. Chen N, Li Q, Yang J, Zhou M, Zhou D, He L. Antiviral treatment for preventing postherpetic neuralgia. *Cochrane Database Syst Rev*. 2014;2:CD006866.

2. Yawn BP, Gilden D. The global epidemiology of herpes zoster. *Neurology*. 2013;81:928–930.

3. Studahl M, Petzold M, Cassel T. Disease burden of herpes zoster in Sweden–predominance in the elderly and in women – a register based study. *BMC Infect Dis*. 2013;13:586.

4. Opstelten W, Mauritz JW, de Wit NJ, van Wijck AJM, Stalman WAB, van Essen GA. Herpes zoster and postherpetic neuralgia: incidence and risk indicators using a general practice research database. *Fam Pract*. 2002;19:471–475.

5. Insinga RP, Itzler RF, Pellissier JM, Saddier P, Nikas AA. The incidence of herpes zoster in a United States administrative database. *J Gen Intern Med*. 2005;20:748–753.

6. Pinchinat S, Cebrián-Cuenca AM, Bricout H, Johnson RW. Similar herpes zoster incidence across Europe: results from a systematic literature review. *BMC Infect Dis*. 2013;13:170.

7. Sundström K, Weibull CE, Söderberg-Löfdal K, Bergström T, Sparén P, Arnheim-Dahlström L. Incidence of herpes zoster and associated events including stroke-a population-based cohort study. *BMC Infect Dis*. 2015;15:488.

8. Anonymus. United Nations Department of Economic and Social Affairs Population Division. *World Popul Ageing*. 2013;2013:ST/ESA/SER.A/348.

9. Dworkin RH, Johnson RW, Breuer J, et al. Recommendations for the management of herpes zoster. *Clin Infect Dis*. 2007;44(Suppl 1):S1–S26.

10. Johnson RW, Rice ASC. Clinical practice. Postherpetic neuralgia. *N Engl J Med*. 2014;371:1526–1533.

11. Wood MJ, Kay R, Dworkin RH, Soong SJ, Whitley RJ. Oral acyclovir therapy accelerates pain resolution in patients with herpes zoster: a meta-analysis of placebo-controlled trials. *Clin Infect Dis*. 1996;22:341–347.

12. Pellissier JM, Brisson M, Levin MJ. Evaluation of the cost-effectiveness in the United States of a vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. *Vaccine*. 2007;25:8326–8337.

13. Dworkin RH, Portenoy RK. Pain and its persistence in herpes zoster. *Pain*. 1996;67:241–251.

14. Oxman MN, Levin MJ, Johnson GR, et al. A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. *N Engl J Med*. 2005;352:2271–2284.

15. Opstelten W, Zuithoff NPA, van Essen GA, et al. Predicting postherpetic neuralgia in elderly primary care patients with herpes zoster: prospective prognostic study. *Pain*. 2007;132(Suppl):S52–S59.

16. Drolet M, Brisson M, Schmader K, et al. Predictors of postherpetic neuralgia among patients with herpes zoster: a prospective study. *J Pain*. 2010;11:1211–1221.

17. Forbes HJ, Thomas SL, Smeeth L, et al. A systematic review and meta-analysis of risk factors for postherpetic neuralgia. *Pain*. 2015;2016;157:30–54.

18. Bouhassira D, Chassany O, Gaillat J, et al. Patient perspective on herpes zoster and its complications: an observational prospective study in patients aged over 50 years in general practice. *Pain*. 2012;153:342–349.

19. Ware JEJ, Kosinski M, Turner-Bowker DM, Gandek B. *User's Manual for the SF-12v2® Health Survey (with a Supplement Documenting SF-12® Health Survey)*. Lincoln, RI: QualityMetric Incorporated; 2002.

20. Szende A, Janssen B, Cabases J. *Self-Reported Population Health: An International Perspective Based on EQ-5D*. Budapest: Springer Open; 2004.

21. Coplan PM, Schmader K, Nikas A, et al. Development of a measure of the burden of pain due to herpes zoster and postherpetic neuralgia for prevention trials: adaptation of the brief pain inventory. *J Pain*. 2004;5:344–356.

22. Hakkaart-van Roijen L, van Straten A, Donker M, Tiemens B. *Handleiding Trimbos/iMTA Questionnaire for Costs Associated with Psychiatric Illness*. Rotterdam: Erasmus University; 2002.

23. Mols F, Pelle AJ, Kupper N. Normative data of the SF-12 health survey with validation using postmyocardial infarction patients in the Dutch population. *Qual Life Res*. 2009;18:403–414.

24. Tukey JW. *Exploratory Data Analysis*. Reading, PA: Addison-Wesley; 1977.

25. Oaklander AL, Bowsher D, Galer B, Haanpää M, Jensen MP. Herpes zoster itch: preliminary epidemiologic data. *J Pain*. 2003;4:338–343.

26. van Wijck AJM, Opstelten W, Moons KGM, et al. The PINE study of epidural steroids and local anaesthetics to prevent postherpetic neuralgia: a randomised controlled trial. *Lancet (London, England)*. 2006;367:219–224.

27. Pica F, Gatti A, Divizia M, et al. One-year follow-up of patients with long-lasting post-herpetic neuralgia. *BMC Infect Dis*. 2014;14:556.

28. Gater A, Abetz-Webb L, Carroll S, Mannan A, Serpell M, Johnson R. Burden of herpes zoster in the UK: findings from the zoster quality of life (ZQOL) study. *BMC Infect Dis*. 2014;14:402.

29. Song H, Lee J, Lee M, et al. Burden of illness, quality of life, and healthcare utilization among patients with herpes zoster in South Korea: a prospective clinical-epidemiological study. *Int J Infect Dis*. 2014;20:23–30.

30. Aunhachoke K, Bussaratid V, Chirachanakul P, et al. Measuring herpes zoster, zoster-associated pain, post-herpetic neuralgia-associated loss of quality of life, and healthcare utilization and costs in Thailand. *Int J Dermatol*. 2011;50:428–435.

31. Laurent B, Vicaut E, Leplège A, Bloch K, Leutenegger E. Prevalence and impact on quality of life of post-herpetic neuralgia in French medical centers specialized in chronic pain management: the ZOCAD study. *Méd Mal Infect*. 2014;44:515–524.

32. Bricout H, Perinetti E, Marchettini P, et al. Burden of herpes zoster-associated chronic pain in Italian patients aged 50 years and over (2009–2010): a GP-based prospective cohort study. *BMC Infect Dis*. 2014;14:637.

33. Pickering G, Leplege A. Herpes zoster pain, postherpetic neuralgia, and quality of life in the elderly. *Pain Pract*. 2011;11:397–402.

34. Ständer S, Zeidler C, Riepe C, et al. European EADV network on assessment of severity and burden of Pruritus (PruNet): first meeting on outcome tools. *J Eur Acad Dermatol Venereol*. 2015;30:1144–1147.