




Determining the Definitive Time Criterion for Postherpetic Neuralgia Using Infrared Thermographic Imaging

Jae Hun Kim · Chang-Soon Lee · Woong Ki Han · Jun Bo Sim ·

Francis Sahngun Nahm 

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ABSTRACT

Introduction: The time criteria used in many studies of postherpetic neuralgia (PHN) are arbitrary and do not have supporting evidence. Therefore, this study sought to determine the definite time criterion for PHN by analyzing the skin temperature to estimate the time point when zoster-induced skin inflammatory reaction ends.

Methods: Infrared thermography was used to measure the difference in skin temperature between the affected and unaffected areas

Jae Hun Kim and Chang-Soon Lee contributed equally to this work and are co-first authors.

The affiliation of Dr. Chang-Soon Lee was changed after the completion of this study.

J. H. Kim
Department of Anesthesiology and Pain Medicine,
Konkuk University School of Medicine, Seoul,
Republic of Korea

C.-S. Lee
Department of Anesthesiology and Pain Medicine,
Seoul National University Hospital, Seoul, Republic
of Korea

W. K. Han
Daeheal Pain Clinic, Seoul, Republic of Korea

J. B. Sim · F. S. Nahm
Department of Anesthesiology and Pain Medicine,
Seoul National University Bundang Hospital,
Seongnam, Republic of Korea

(Δ Temp) in the craniocervical and thoracic regions of patients with herpes zoster (HZ). Because the Δ Temp changes from a positive value to zero when the skin is no longer inflamed, a Δ Temp ≤ 0 was defined as the end of skin inflammation, and this time point was considered the starting point for PHN. This cutoff time point was estimated using receiver operating characteristic (ROC) curve analysis.

Results: A total of 503 patients were included in this study. The ROC curve analysis showed that the time point when the Δ Temp was ≤ 0 occurred at 12 weeks after HZ onset (95% confidence interval 11–15 weeks, area under the ROC curve 0.901). Using this time point as the time criterion of PHN, the sensitivity, specificity, and classification accuracy were 0.807, 0.905, and 0.871, respectively.

F. S. Nahm (✉)
Department of Anesthesiology and Pain Medicine,
Seoul National University College of Medicine, 103
Daehak-ro, Jongno-gu, Seoul 03080, Republic of
Korea
e-mail: hiitsme@snuh.org

Present Address:
C.-S. Lee
Pyeonhan-nail Pain Clinic, Seoul, Republic of Korea

Conclusions: The transition of skin temperature from warm to cold occurs 12 weeks after HZ onset, which implies the end of local inflammation. Therefore, PHN associated with pathophysiologic change may be defined as 12 weeks after the skin rash. This finding provides a theoretical basis for the timing definition of PHN.

Keywords: Herpes zoster; Inflammation; Postherpetic neuralgia; Pathophysiology; ROC curve; Skin

Key Summary Points

Why carry out this study?

Although various time criteria for postherpetic neuralgia (PHN) are used, these are arbitrary and lack supporting evidence.

This study aimed to determine the time criterion of PHN by objectively analyzing the skin temperature to estimate the time point when the skin inflammatory reaction ends.

What was learned from this study?

The infrared thermographic image analysis showed that the transition of skin temperature from warm to cold occurs 12 weeks after herpes zoster onset (95% confidence interval 11–15 weeks, area under the receiver operating curve 0.901).

This time point was considered the starting point for PHN.

These findings serve as a theoretical basis for the timing definition of PHN.

varicella-zoster virus [1]. It is crucial for herpes zoster (HZ) to be distinguished from PHN because differences in their pathophysiology require different treatments. In the early HZ stage, pain is accompanied by severe inflammation of the skin, peripheral nerves, and dorsal root ganglia. In the late PHN stage, histopathologic changes occur in the affected peripheral and central nervous system [2–4]. There is even a report of a patient suffering from PHN with a neuropathic itch in the area where 96% of the epidermal innervation was lost [5].

Although the term PHN is used after a certain point during the course of the disease, the time point for PHN during the transitional process from HZ to PHN remains unclear [6]. Literature on the diagnostic criteria for PHN shows no consensus on the time point after HZ onset when the disease can be considered PHN. Various time criteria for PHN have been used, such as 30 days after initial HZ onset [7], pain lasting for ≥ 1 month following healing of the rash [8], pain persisting 90 days after the onset of vesicles [9], or pain lasting for 3 months after the end of the acute period (approximately 4 months from HZ onset) [10]. Furthermore, these time criteria for PHN lack supporting evidence and are arbitrary. Statistical modeling has also been used in an attempt to define PHN, and it was concluded that PHN occurred at 110.3 ± 11.9 days after the rash [11] or 120 days after rash onset [12]. However, these statistical models were based only on the patients' symptoms and did not consider objective findings. Owing to the lack of consensus on the time criterion for PHN, the following simple definition of PHN was used: pain that persists after the skin eruption has been resolved [13]. Because the time criterion of PHN is arbitrary, these definitions cause much confusion in further studies on PHN since the incidence and prevalence of PHN varies by definition [14]. Therefore, it is crucial to define a more objective and accurate time criterion for PHN that is based on supporting objective evidence.

Several studies have used infrared thermography (IRT) to measure skin temperature during HZ-affected periods [15–17]. IRT is a noncontact imaging technique that uses an infrared camera to detect and visualize emitted body heat. The

INTRODUCTION

Postherpetic neuralgia (PHN) is a chronic neuropathic disease where patients experience severe pain after a skin lesion outbreak due to either initial infection or reactivation of

obtained images are used to detect physiologic and functional abnormalities. IRT can be utilized to evaluate neurologic, vascular, and musculoskeletal diseases affecting regional skin temperature or the effect of a sympathetic block [18]. It is highly sensitive for the diagnosis of neuropathic pain [19] and is a reliable method for detecting various pain disorders [20, 21].

IRT determines abnormalities based on the phenomenon that the skin temperatures on left and right sides of the body are symmetrical in normal conditions. Therefore, asymmetry of skin temperature of the region of interest versus the contralateral side (Δ Temp) suggests an abnormality [22, 23]. Hot spots on the IRT image, which represent elevated skin temperature, appear when inflammatory mediators are released due to local inflammatory reactions, and cold spots appear due to sympathetic activation [18]. In the early phase of HZ, the skin temperature rises due to inflammatory reactions in the affected area and followed by the typical healing process, in which the symmetry of the skin temperature is restored after clinical resolution of the affected area [24]. However, in the chronic stage of PHN, skin temperature asymmetry is accompanied by low-temperature lesions due to sympathetic activation, appearing as cold spots in IRT images [15, 18], which implies the involvement of a neuropathic complication [17]. Therefore, it can be inferred that the time point at which the hot spots change to cold spots indicates the transition from HZ to PHN, and this can be observed using IRT.

From these phenomena, it was postulated that if inflammatory reactions are present, the skin temperature of the affected area would be warm, gradually decreasing to normal as the inflammation resolves, and then become colder than the unaffected area if sympathetic activation occurs. The objective of this study was to determine the time criterion of PHN by analyzing the skin temperature to estimate the time point at which the skin inflammatory reaction ends.

METHODS

Patients

This was a multicenter retrospective cohort study conducted at three university-affiliated hospitals in South Korea. This study was approved by the institutional review board of Seoul National University Bundang Hospital (approval number: B-2006/616-404), Seoul National University Hospital (approval number: H-1907-159-1050) and Konkuk University Hospital (approval number: KUMC 2019-09-027). Given the retrospective nature of this study and the use of anonymized patient data, the requirement for informed consent was waived. All procedures were carried out in accordance with the Helsinki Declaration of 1964 and its subsequent amendments.

The inclusion criteria were patients who visited one of the pain centers at the three university-affiliated hospitals with the complaint of pain after HZ in the craniocervical and thoracic dermatome between March 2013 and February 2019. The exclusion criteria were (1) patients with herpes zoster bilateralis; (2) patients who underwent interventional treatments, including epidural injections, intercostal nerve block, sympathetic block, paravertebral block, or radiofrequency lesioning at the affected nerves due to HZ-related pain; (3) patients whose IRT image was unavailable or where the regions of interest on the IRT image were incorrect; (4) patients who had an operation scar on the HZ-affected skin lesion; (5) patients with radiating pain on upper extremities due to a herniated intervertebral disc or spinal stenosis, and (6) patients with a history of cerebrovascular accidents or tumor in the brain or spinal cord.

Measurement of Skin Temperature

Skin temperature was measured using a standard IRT protocol [20, 25]. The patient was acclimatized in an isolated space for 20 min at an average room temperature of 23 ± 1 °C (relative humidity, 50%) without clothing. IRT images were then taken using a digital infrared

thermal imaging system (T-1000 Smart[®], Mesh Co., Ltd., Wonju, Korea) consisting of a computer-assisted infrared camera and a display module. This device can detect infrared energy emitted from the skin using a focal plane array sensor (detection range, 14.5–40.0 °C, sensitivity: ≤ 0.05 °C, frame rate: 30 frames/s). The display module visualized thermal differences in 256 color levels with a resolution of 640×480 pixels. The patient stood 1 m away from the IRT device and IRT images were taken from the back, front, and both sides of the body. The skin temperature difference between the affected and contralateral unaffected regions was calculated using the following formula:

$\Delta\text{Temp} = \text{skin temperature on the affected region} - \text{skin temperature on the contralateral region}$.

In accordance with a previous study [20], multiple ΔTemps were determined for each patient. The ΔTemp with the maximum absolute value ($|\Delta\text{Temp}|$) was chosen as the representative value of their skin temperature abnormality. Figure 1 presents an example IRT image.

Statistical Analysis

ΔTemp changes from a positive value to zero when inflammation caused by HZ in the skin ends and then progresses to a negative value due to the onset of PHN. Therefore, $\Delta\text{Temp} \leq 0$ was defined as the end of skin inflammation, and this time point was considered the starting point for PHN. The optimal cutoff time point for the end of skin inflammation ($\Delta\text{Temp} \leq 0$) was estimated using the receiver operating characteristic (ROC) curve analysis to maximize the classification accuracy and Youden's J statistics. Furthermore, the 95% confidence intervals (CIs) for this cutoff time point and Youden's J statistics were calculated using the bootstrapping method introduced by Matsumoto et al. [26] with 5000 iterations and 978 as the random number seed. The required sample size was calculated using the following conditions based on the pilot observation: (1) $\alpha = 0.05$ and power $(1 - \beta) = 0.9$ for the one-tailed test, (2) estimated area under the ROC

curve (AUC) = 0.8 and null hypothesis value for AUC = 0.7, and (3) estimated ratio of sample sizes in the negative/positive groups = 4. These conditions resulted in a total sample size of 475 patients. For subgroup analysis, the patients were categorized into two groups: patients with zoster-related pain in the craniocervical region (C group) and those with zoster-related pain in the thoracic region (T group).

The G*power version 3.1.0 software (Heinrich-Heine-Universität Düsseldorf, Germany) was used for sample size calculation. The NCSS 2021 statistical software, version 21.0.2 (NCSS LLC., Kaysville, UT), and MedCalc v19.1.7 (MedCalc Software Ltd., Ostend, Belgium) were used for the statistical analysis. A *P* value of < 0.05 was considered statistically significant.

RESULTS

A total of 503 patients were included in this study. Table 1 summarizes patient demographics. The distribution of the ΔTemp over the duration of the disease is presented in Fig. 2a. The ΔTemp initially showed a positive pattern in the early phase of HZ, then gradually decreased and became negative. Figure 2b shows the mean \pm standard deviation of the ΔTemp over time. The ROC curve analysis revealed that the time optimal cutoff point at which the ΔTemp became negative was 12 weeks (95% CI 11–15 weeks, Fig. 3). Furthermore, the ΔTemp before and after this cutoff point showed a significant difference ($P < 0.001$). When this time point was used as the time criterion of PHN, the sensitivity and specificity were 0.807 and 0.905, respectively. Both Youden's J index (0.712) and classification accuracy (0.871) were highest at the time point of 12 weeks. The area under the curve was 0.901 (95% CI 0.866–0.927), which was statistically significant ($P < 0.001$). Subgroup analysis showed results similar to the above findings: the optimal cutoff point for determining the PHN for C and T groups was 11 and 12 weeks, respectively. Table 2 presents the results of the subgroup analysis.

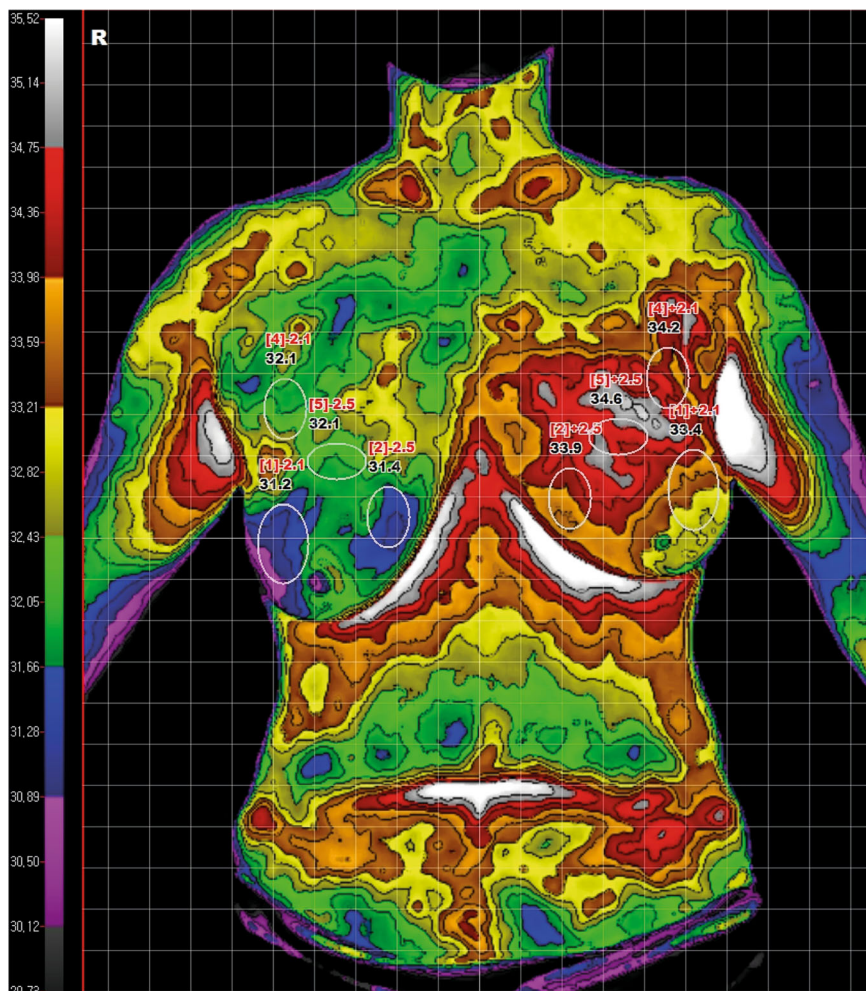


Fig. 1 Representative infrared thermographic (IRT) image of a patient with zoster-related pain. The patient experienced pain in the right breast 24 weeks after zoster

outbreak, and the IRT shows decreased skin temperature (-2.5°C) in the right breast compared with the contralateral side

DISCUSSION

The results of this study revealed that the time point of the start of PHN was 12 weeks after HZ onset. This is consistent with a PHN definition previously used: 3 months after the onset of skin rash [14]. Furthermore, the 3-month period is the same time period for defining chronic pain [27]. Various time criteria for PHN have been used arbitrarily and without a rationale [6, 7, 10, 11, 28, 29]. Meanwhile, the present study provides a standard time criterion with a pathophysiologic basis.

The asymmetric temperature of HZ lesions has been reported [17, 24, 30–32], with a higher skin temperature in the early phase of HZ and the thermal patterns correlating well with the duration of the disease [31]. However, the association between temperature changes and disease duration was not investigated. To the best of our knowledge, this is the first study to measure changes in skin temperature over the disease duration and is the largest study of the relationship between skin temperature and zoster-related pain.

IRT, a noninvasive technique that accurately detects temperature changes, was used to

Table 1 Demographic data of the patients included in this study ($N = 503$)

Variable	Values
Age (years)	66.4 ± 13.3 (range, 17–92)
Sex (male/female)	230 (45.7%)/273 (54.3%)
Affected region	
Craniofacial	62 (12.3%)
Cervical	59 (11.7%)
Thoracic	382 (76.0%)
Median period after skin lesion (weeks)	5 (range 0.5–416)

Values are presented as the mean ± standard deviation or the number (%) of patients

measure skin temperature. IRT shows physiologic abnormalities and allows the objective visualization of subjective symptoms. Furthermore, it can be used to diagnose and monitor neuropathic diseases [33] and has a greater sensitivity compared with the sympathetic skin response test in diagnosing neuropathic pain [19]. It was suggested that inflammation associated with a virus infection and nerve damage,

or vasodilatation associated with neurosecretion from hyperactive nociceptors in the acute phase, causes regional hyperthermia, resulting in warm spots on IRT images [18]. In contrast, vasoconstriction associated with sympathetic overactivation related to denervation in the chronic phase causes hypothermia, resulting in cold spots on IRT images [24]. Therefore, IRT has been used to assess skin inflammation in cases of HZ, and its usefulness has been well demonstrated [15, 17, 34–36].

The pathophysiology of the pain differs in early HZ and in that of PHN. In the early HZ stage, blistering skin eruptions and intense inflammation of the affected skin and nerves result in higher temperatures in the affected area compared with the unaffected side [17]. However, there is no local inflammatory reaction in the PHN stage. Instead, pain from PHN is caused by deafferentation, manifested as sensory loss, and sensitization of intact nociceptors, manifested as hyperalgesia [37]. Additionally, concomitant central sensitization related to secondary changes or damage in the spinal cord dorsal horn and hyperactivity of central pain transmission neurons can result in severe pain in PHN [38, 39]. These pathophysiologic differences between the HZ and PHN stages mean that treatment options differ between the earlier HZ stage and PHN.

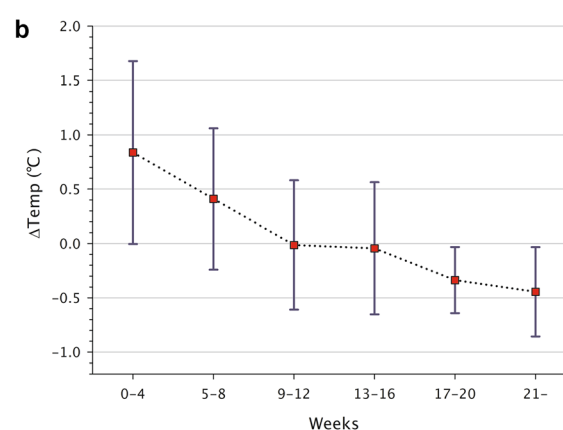
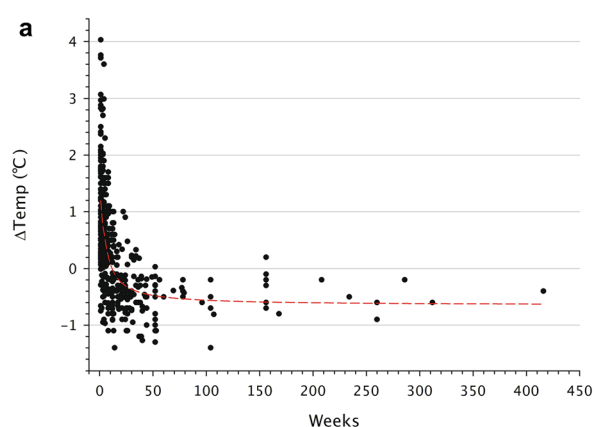


Fig. 2 Distribution of the skin temperature difference between the affected and unaffected sides (ΔTemp) caused by herpes zoster over time. The ΔTemp tends to gradually decrease over time. **a** Scatter plot representing the ΔTemp

over time (weeks). The red line shows the fitted curve for the data. **b** Line plot representing the mean ± standard deviation of the ΔTemp at each time period

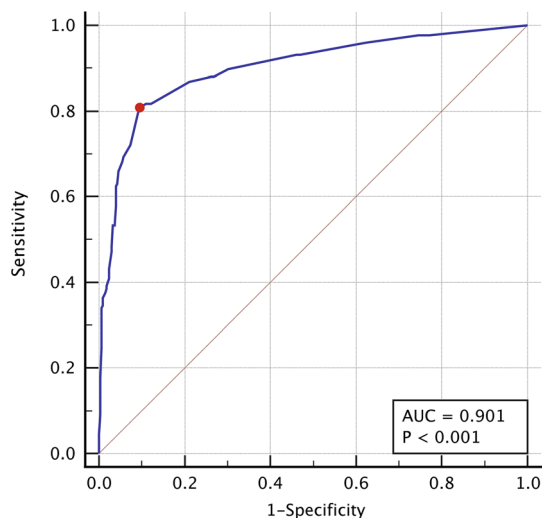


Fig. 3 Receiver operating characteristic (ROC) curve analysis to determine the timing criterion of cessation of skin inflammation in herpes zoster. The *red dot* on the ROC curve indicates the optimal cutoff point at which the transition of skin temperature from warm to cold occurs after herpes zoster onset (12 weeks: sensitivity 0.807 and specificity 0.905). At this point, Youden’s J index (0.712) and classification accuracy (0.871) were the highest

In the early stage, the administration of antiviral medication within 3 days after the skin rash is crucial for treating HZ and preventing PHN [40]. Although glucocorticoids can be used in the early stage to reduce pain and promote early healing by reducing acute inflammation, they do not prevent PHN [38, 40]. A systematic

review reported that interventional treatments, such as subcutaneous injections of local anesthetics and steroids as well as paravertebral block and continuous or repeated epidural block, in the early stage could reduce HZ-related pain and prevent PHN [28, 38, 41, 42]. A steroid injection to the affected nerve root was reported to show a good effect in the early stages of HZ, but its effectiveness gradually decreases over time. A recent study reported that the golden period for a steroid injection to the affected nerve root to be effective was within 12 weeks of HZ onset [43]. This phenomenon is exactly in line with our study findings because the anti-inflammatory effect of steroids and steroid injection to the affected nerve root showed a good effect within 12 weeks. However, because the inflammatory reaction ends 12 weeks after HZ onset, the steroid effect of injection to the damaged nerve root would decrease after 12 weeks. In contrast to the early stage, anti-convulsants, tricyclic antidepressants, serotonin/norepinephrine reuptake inhibitors, opioids, tramadol, topical lidocaine, and topical capsaicin are used to treat PHN [14, 38, 41].

This study has some limitations. First, the skin temperature was not measured sequentially in each patient. Although this would be best, it is impossible to observe the natural course of skin temperature change over time without any interventional or medical treatment after shingles due to ethical and practical reasons. Second, this study did not consider patients’

Table 2 Optimum cutoff time point for the end of skin inflammation ($\Delta\text{Temp} \leq 0$) and associated statistics

Statistics	Total number of patients ($N = 503$)	C group ($N = 121$)	T group ($N = 382$)
Cutoff time point (95% CI)	12 (11–15) weeks	11 (10–15) weeks	12 (11–15) weeks
Sensitivity (95% CI)	0.807 (0.741–0.862)	0.826 (0.612–0.951)	0.804 (0.732–0.864)
Specificity (95% CI)	0.905 (0.868–0.935)	0.959 (0.899–0.989)	0.882 (0.833–0.921)
Accuracy (95% CI)	0.871 (0.838–0.899)	0.934 (0.874–0.971)	0.851 (0.811–0.885)
Youden’s J index (95% CI)	0.712 (0.637–0.770)	0.785 (0.578–0.913)	0.686 (0.600–0.752)
AUC (95% CI)	0.901 (0.866–0.927)	0.897 (0.744–0.960)	0.896 (0.857–0.925)

This time point was estimated using the receiver operating characteristic curve to maximize the classification accuracy and Youden’s J index

C group patients with zoster-related pain in the craniocervical lesion, *T group* patients with zoster-related pain in the thoracic region, *AUC* area under the curve, *CI* confidence interval

symptoms, which would have been better. However, a previous study has already evaluated patient symptoms and defined PHN through statistical modeling [11]. The present study aimed to estimate the time point of skin inflammation change using an objective measurement. Third, this study focused on the changes in the skin temperature and did not consider changes in the central nervous system. The pathologic changes of PHN that occur in peripheral nerves and dorsal root ganglia may result in central sensitization. Many neuroimaging studies on HZ and PHN have demonstrated abnormalities in the function and structure of the brain [44, 45]. Although the association of skin temperature and central sensitization in patients with PHN has not been reported, excessive vasoconstriction has been observed due to enhanced sympathetic outflow after spinal cord injury [46]. Furthermore, it was reported that autonomic disturbance could occur in patients with central pain syndrome, and the skin temperature was significantly cooler in the affected area due to cutaneous vasoconstriction [47]. Therefore, we believe that changes in the central nervous system may affect sympathetic activation, which is eventually reflected in the corresponding skin temperature. Further investigation is necessary to demonstrate the relationship between changes in the central nervous system and skin temperature in PHN.

CONCLUSIONS

The transition of skin temperature from warm to cold occurs 12 weeks after HZ onset, which suggests that the cutaneous inflammatory reactions end at this time point. Therefore, the definition of PHN associated with pathophysiologic change is 12 weeks after the skin rash. The authors believe this finding serves as a theoretical basis for the timing definition of PHN.

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Author Contributions. Conceptualization: FSN; data collection: FSN, JHK, and C-SL; data analysis: FSN; writing—original draft preparation: JHK and CSL; writing—review and editing: WKH and JBS; supervision: FSN.

Disclosures. Jae Hun Kim, Chang-Soon Lee, Woong Ki Han, Jun Bo Sim, and Francis Sahn-gun Nahm have nothing to disclose.

Compliance with Ethics Guidelines. This study was approved by the institutional review board of Seoul National University Bundang Hospital (approval number: B-2006/616-404), Seoul National University Hospital (approval number: H-1907-159-1050) and Konkuk University Hospital (approval number: 2019-09-027). All procedures were performed in accordance with the Helsinki Declaration of 1964 and its later amendments. Given the retrospective nature of this study and the use of anonymized patient data, the requirement for informed consent was waived.

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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