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A Prognostic Score for Postherpetic Neuralgia in Ambulatory Patients

Summary: The main objective was to develop a scoring system for easy use by the physician in daily clinical practice in deciding the appropriate treatment for his herpes zoster patient. Data from 635 patients who did not receive antiviral therapy were included in this analysis. Of these, 131 developed postherpetic neuralgia (PHN). Of the 29 variables tested univariately in this study, 15 showed a significant correlation with the incidence of PHN, but only six proved to contribute to the overall predictive power in the multivariate approach. Using two independent approaches, the model showed a very satisfactory performance in the validation sample. Patients without acute pain rarely developed PHN. In those with acute pain, being female, being over 50 years of age, having more than 50 lesions, having lesions of a hemorrhagic nature, having cranial or sacral localisation of the rash or having pain in the prodromal phase proved to be significant, multivariate factors. An easy-to-use scoring system used in a risk graph is proposed. These data should be useful in the individual treatment decision as well as in the design and analysis of therapeutic trials in herpes zoster.

Introduction

Up to 20% of the general population will experience an episode of herpes zoster during its lifetime [1]. The most important and costly complication of this disease is postherpetic neuralgia (PHN), a serious and frustrating medical problem [2–4]. PHN is reported to occur in 10–70% of zoster patients [2, 3, 5].

A prospective physician-based epidemiologic study was conducted in ambulatory patients with zoster in Germany [6]. In the subset of patients without systemic antiviral therapy, potential risk factors were evaluated. Prognostic factors are also very important in the design, conduct and analysis of clinical trials, because they can improve stratification, facilitate the correction of imbalances and increase statistical power. Finally, prognostic factors may stimulate research concerning the still unclear pathophysiology of PHN [2, 5].

Methods

General study plan: A prospective, observational study surveyed the epidemiology of ambulatory patients with the clinical diagnosis of herpes zoster [6]. Planning of the study was done by the German Study Group Zoster*, conduct and analysis of the data by the independent "Gesellschaft für Angewandte Mathematik und Informatik (gmi)." A representative sample of family physicians, dermatologists and specialists in internal medicine across Germany were asked to participate. Demography, history, symptoms of a prodromal phase, characterisation of pain, other clinical symptoms, description of the cutaneous lesions and the therapy planned were asked at the patient's first visit. Patients were included irrespective of their treatment and physicians did not receive any guidance concerning their individual treatment decisions. We prospectively restricted the evaluation of risk factors to patients not receiving systemic antiviral therapy. The second visit was planned at the time of crusting of the lesions. Four to 5 weeks after complete crusting had occurred, the physician was asked to document the presence of pain (constituting the diagnosis of PHN). To avoid unnecessary patient visits, the physician could obtain this information over the telephone.

Sample size: For the sample size estimate, at least ten events of PHN are needed to identify one variable as a prognostic factor [7]. The objective was to find no more than ten prognostic factors; assuming an average incidence of PHN of 20%, we aimed to include at least 500 patients with zoster who did not receive antiviral therapy.

Data collection: At the first visit, the following data were collected: sex, age, relevant patient history (e.g. malignant disease, allergy, immunosuppressive therapy), presence and duration of prodromal signs and symptoms (e.g. elevated body temperature, dermatomal pain, malaise, nonspecific flu-like pain), and descriptive data of disease (localisation of cutaneous lesion, extent of skin affected (or does this refer to the number of dermatomes

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Table 1: Univariate and multivariate correlations between prospectively defined signs and symptoms during first visit and occurence of PHN.

		P values	
		Univariate	Multivariate
Demographics	Age	0.001	0.002
	Sex	0.010	0.004
	Speciality of treating physician	n.s.	n.s.
History	Malignancy	0.002	n.s.
	Diabetes mellitus	0.001	n.s.
	Allergy type I–III	n.s.	n.s.
	Allergy type IV	n.s.	n.s.
	Neurodermatitis	n.s.	n.s.
	Radio/chemotherapy	n.s.	n.s.
	Immunosupressive therapy	n.s.	n.s.
	Operation/physical trauma	n.s.	n.s.
	Life event	n.s.	n.s.
	HIV positive	n.s.	n.s.
	Pregnancy	n.s.	n.s.
Prodromal phase	Body temperature > 37°C	n.s.	n.s.
	Nocturnal sweating	0.021	n.s.
	Pain/burning in dermatome	0.001	0.001
	Nonspecific pain	0.001	n.s.
	Paresthesias	n.s.	n.s.
	Fatigue	0.001	n.s.
	Nausea	0.001	n.s.
	Lymph node swelling	n.s.	n.s.
Description of zoster	Localisation*	0.001	0.04
	Extension of lesions	0.006	n.s.
	Number of lesions	0.001	0.003
	Hemorrhagic lesions	0.001	0.03
	Acute zoster pain	0.001	**
Therapy before first visit	Analgesics	0.002	n.s.
	Antidepressant drugs	n.s.	n.s.

n.s. = non significant; * localisation = the localisations were grouped in two categories: high risk (cranial, sacral) and low risk (cervical, thoracal, lumbar); ** this variable was not included in the multivariate analysis since patients without it have a negligible risk for PHN. Restricting the analysis to the patients with pain enhanced the power of the model. In case of inclusion, it would have been significant.

affected?), number of lesions, size of lesion, intensity of zoster-related pain and others).

A second visit was scheduled at the time of lesion crusting. The following data were collected: manifestations of disease (number of lesions, time-point of crusting, zoster-related pain, complications e.g., spread to additional dermatomes, ophthalmological complications, paresis).

Finally, the occurrence of postherpetic neuralgia was assessed; 4–5 weeks after crusting the physician ascertained the presence/absence of pain in the afflicted area.

Development of the model: Patient variables assessed at the first visit were considered to be candidates for prognostic factors (Table 1). Continuous and multicategorical variables (e.g. age, temperature, number of lesions, localisation) were dichotomized to construct a simple formula for the score.

To select factors for modelling, a univariate correlation analysis was performed between each individual factor and the occurrence of PHN. If a univariate correlation was significant ($P<0.05$), the factor was included in a stepwise selection procedure to evaluate the final set of multivariate factors and their coefficients for the logistic regression model predicting the risk of PHN. SAS software was used for the statistical computations (SAS-Institute; SAS release 6.10; # Cary, N.C.: 1994).

Validation of the model: The total sample of untreated patients was divided into the training sample and the validation sample in a proportion of 3:1.

The individual probability for developing PHN was calculated for each patient of the validation sample by using the result of the model developed in the training sample. According to the estimated probabilities, the patients were divided into five equal size groups by the appropriate quintiles of the distribution of these probabilities. For each group, the expected and observed numbers of cases of PHN were compared. The expected number of PHN cases in a particular group was calculated as the sum of the probabilities for the occurrences of PHN summarised of all members of this group.

To show the information gain of our model, we calculated the ROC curve using all patients in the validation sample [8, 9].

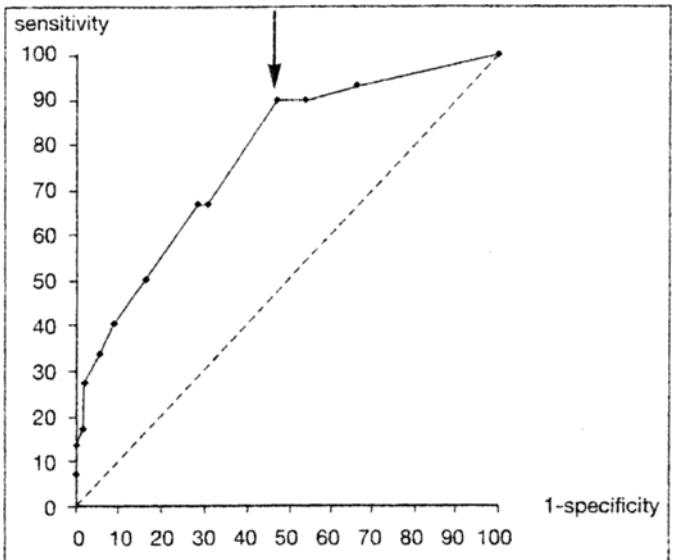
Results

Sample Description

Four hundred and eighty-six physicians provided patient data. A total of 635 patients who did not receive antiviral

Table 2: Observed and expected PHN cases in the five strata of the independent validation sample defined by the PHN risk showing excellent agreement.

Stratum	n	Observed number of cases	Expected number of cases
1	24	0	0.4
2	30	2	1.5
3	32	5	4.0
4	33	8	8.5
5	32	15	16.3



→: cutoff point mentioned as example in the text. The area between the curve and the line of identy represents the information gain.

Figure 1: Validation of the model: ROC curve.

therapy were included in this analysis, of whom 131 developed PHN. Fifty-six percent were female. The age distribution of the sample was similar to that of the total population but with a slight skew to higher incidences below the age of 30 years [6]. Malignancies were reported in 24 patients, insulin treated diabetes mellitus in 30 patients, allergies in 90 patients, neurodermatitis in 43 patients, immunosuppressive therapy in 11 patients, HIV positivity in one patient and pregnancies in nine patients. The most frequent prodromal symptom was pain or burning sensation in the affected dermatome (73%). Thirteen percent of patients reported nocturnal sweating and 27% reported nonspecific flu-like headache or limb pain.

The zoster rash was localised cranially in 10% of patients and at the thoracic dermatomes in 53% of patients. Cervical, lumbar and sacral dermatomes were affected in 11%, 21% and 8% of patients, respectively. In 75% of patients, the zoster rash was restricted to one dermatome and to two adjacent dermatoma in 24% of cases. Disseminated zoster occurred only rarely and lesions were hemorrhagic in 13% of cases.

Although systemic antiviral therapy was excluded, 47% of the patients received other systemic therapy, especially analgesics.

The training and validation samples consisted of 477 and 158 patients, respectively.

Development of the Model

The results of the univariate analyses are summarised in Table 1. It should be noted that the univariate analysis may lead to erroneous conclusions due to correlations between the individual risk factors. Of fifteen significant factors in the univariate analysis, only the following six showed a significant influence using the correct multivariate analysis: sex, age, number of lesions, localisation, hemorrhagic lesion, and pain in the prodromal phase. Ninety-six percent of patients who did not report pain at the first visit did not develop PHN. This allowed us to restrict our model building using a stepwise logistic regression procedure to those patients with pain at the first visit.

The patient with the highest risk for PHN can be described as follows: pain at the first visit, female, over 50 years old, more than 50 hemorrhagic lesions, an affliction in the cranial or sacral area and dermatomal pain in the prodromal phase.

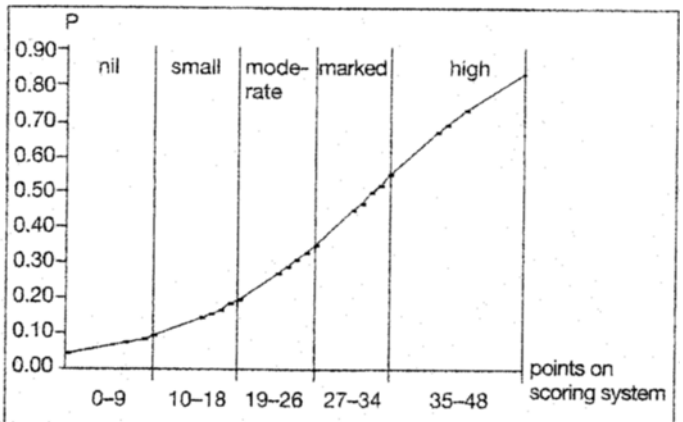
Validation of the Model

In the validation sample, the validity of the model was tested by two approaches.

1) The comparison of expected to observed cases in the five quintiles of risk showed excellent agreement (Table 2).

2) The ROC curve (based on the logistic formula for predicting PHN) showed a marked increase of information represented by the area between the line of identity and the curve (Figure 1).

The clinical relevance of the ROC curve can best be explained by choosing a specific point on the curve. With the cutoff point (risk of PHN yes or no) given as an example in Figure 1, a sensitivity of 93% with a specificity of 42% could be attained. In other words: using the cutoff point, this model would correctly predict 93% of true positives (i.e. a positive prediction by the model of those developing PHN) at the cost of 58% false positives (patients with a positive prediction by the model who did not develop PHN). For the clinical setting of herpes zoster, a risk prediction with these characteristics should be very helpful in making decisions. If this cutoff point was to be used as the treatment decision point at the patient's first visit, then only every 15th patient developing PHN would not have re-



P = the risk of developing PHN for an individual patient. nil ... high is arbitrarily assigned by the authors, to make the risks more tangible. The triangles represents all numerical values the score can assume, the values were used to construct the curve.

Figure 2: Approximate risk of PHN according to score.

ceived treatment and every other patient would have been treated unnecessarily.

User-Friendly Application of the Model

A proposed scoring system for practical use based on the regression coefficients is summarised in Table 3. An individual score for each patient can be computed by summation.

This score could then be transferred easily into a graphical presentation, relating it to the categorised risk level of developing PHN (Figure 2).

Discussion

Zoster is a self-limiting disease which generally lasts only 3 to 4 weeks and tends not to recur in the immunocompetent patient. There is, however, the troubling condition of postherpetic neuralgia (PHN) which, in some patients, can be resistant to analgesic therapy. PHN causes great distress to the patient, to his family and to the physician. The pathophysiology is still unclear. Therapy is based on tricyclic antidepressants, carbamazepine, topical anaesthetic ointment and nonpharmacological approaches, but remains unsatisfactory [5, 10]. Alternative unproved healing methods are used by patients as a last resort.

A landmark-paper described being a woman or elderly as risk factors for the development of this complication [11]. A recent multivariate analysis has added prodromal symptoms as a risk factor [15]. Other risk factors have been proposed including psychosocial variables [3, 12]. Recent studies have shown that timely antiviral systemic therapy can influence the duration of pain and this has renewed interest in the predictability of postherpetic pain [13, 14]. In a double-blind, randomised, placebo-controlled study, famciclovir given three times daily at a dose of 500 or 750 mg, significantly reduced the duration of postherpetic

Table 3: Proposed scoring system for calculating the individual PHN risk for a patient with acute zoster pain.

Female	8
Age > 50 years	9
Number of lesions ≥ 50	8
High-risk localisation (cranial/sacral)	6
Haemorrhagic lesions	8
Dermatomal pain in prodromal phase	9

The coefficients of the multivariate regression were translated into these score values. If a condition is met, add the apropriate figure, if not add 0. The sum is then used in Figure 2.

neuralgia by approximately 2 months (median) [13]. In a large comparative trial of valaciclovir and aciclovir, a 7-day treatment with valaciclovir accelerated the resolution of pain that persisted for more than 30 days as compared with acyclovir [14].

In a large survey in ambulatory patients, 468 office-based physicians referred a total of 2,063 patients with zoster [6]. A main objective of this survey was the quest for a set of predictive factors for PHN, definable at the first visit. Although clinical trials have yielded conflicting results for systemic antiviral therapy in preventing PHN, such therapies could be a major confounding factor. Therefore our analysis was restricted to those patients not receiving any systemic antiviral therapy.

Previous analyses of predictive variables mostly used the univariate approach.

Out of the 29 variables tested univariately in this study, 15 showed a significant correlation with the incidence of PHN (Table 1).

A lack of correlation does not necessarily imply a lack of biological association: possibly the data do not suffice to address this question. This is, for example, the case with the candidate risk factors HIV-positive or immunosuppressive therapy – well-known risk factors [15]. Not enough patients were reported in this ambulatory setting to yield statistical results for this. Conversely, a risk variable may be part of the model in spite of questionable biological relevance. For example, the variable "sex" is important in our mathematical model (which the data used, with the categorisation as done etc.) without necessarily implying a biological relevance. To test this, an universal risk factor analysis correcting for all confounding variables would be preferable.

Patients without pain at the first visit have a negligible risk of PHN; therefore the decision was taken to develop the multivariate model for the patient with acute pain at first presentation.

Only six of the 15 variables, which were significant in an univariate analysis, proved to contribute to the overall predictive power in the multivariate approach. This difference shows that a univariate analysis may lead to the wrong conclusions. For example, diabetes mellitus is included in the univariate prediction but excluded in the multivariate prediction. Presumably, the high correlation

of diabetes mellitus with age leads to this spurious result as age is one of the variables in the multivariate model.

Although many textbooks remind the reader that even patients with mild lesions may develop PHN, the model demonstrates that the more severe the lesions are, the greater is the likelihood of PHN.

The magnitude of the influence in this model is reflected by the odds ratios. Age and pain in the prodromal phase have a strong influence, and localisation of the rash has a moderate influence.

Using two independent approaches, the model showed a very satisfactory performance, suggesting its suitability for clinical research as well as clinical practice. Since multiple regression is not very practical for everyday use, we translated it into a scoring system (Table 3).

Using five ranges, the scoring system can be easily translated into a risk graph (Figure 2).

Our data do not indicate when to treat an individual patient. This decision requires not only consideration of such factors as the patient-physician relationship, but also considerations related to cost-effectiveness and a consensus on the influence of systemic antiviral therapy on PHN.

In conclusion, a multivariate, predictive model was developed for the risk of PHN occurrence in patients with acute herpes zoster. To achieve this, we used prospectively collected data during the first visit when zoster was diagnosed in a large sample of patients who did not receive any systemic antiviral therapy. A risk assessment at this time is needed since early antiviral therapy is more promising than later intervention [13, 14]. Patients without acute pain rarely developed PHN. In those with acute pain, women over the age of 50 years, number of lesions, a hemorrhagic nature of lesions, a cranial or sacral localisation and pain in the prodromal phase proved to be significant, multivariate factors. For better practical use, we translated this into a scoring system combined with an easy-to-use graphical interpretation. These data should be useful in the individual treatment decision as well as in the design and analysis of therapeutic trials in herpes zoster.

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