

# Can a Pretreatment Visual Analog Scale Predict Treatment Outcome in Allergic Rhinitis?

Virat Kirtsreesakul Jitanong Leelapong Suwalee Ruttanaphol

Department of Otolaryngology, Faculty of Medicine, Prince of Songkla University, Hat Yai, Thailand

## Keywords

Allergic rhinitis · Nasal symptom · Predictive value · Treatment outcome · Visual analogue scale

## Abstract

**Background:** The visual analogue scale (VAS) is a simple and useful tool to assess the severity of allergic rhinitis. Whether a pretreatment VAS score can guide appropriate medication is unclear. **Objective:** The aim of this study was to evaluate whether a pretreatment VAS score could be used to predict therapeutic response. **Methods:** A prospective 4-week cohort study involving 101 allergic rhinitis patients was carried out. All patients were treated with triamcinolone acetonide aqueous nasal spray 220 µg once daily for 28 days. The treatment outcomes were evaluated using VAS scores (0–10 cm), total nasal symptoms scores (TNSSs), nasal mucociliary clearance times (NMCCTs), and global symptom controls (GSCs). The minimal clinically important differences (MCIDs) method was used to separate the patients into with and without improvement groups. Receiver operating characteristic curve analysis was performed to evaluate the predictive value of pretreatment VAS scores in relation to MCIDs after treatment. **Results:** Pretreatment VAS scores showed a positive correlation with pretreatment TNSSs and NMCCTs ( $p = 0.66$ ,  $p < 0.001$  and  $r = 0.44$ ,  $p < 0.001$ , respectively), and a

negative correlation with GSCs after treatment ( $r = -0.53$ ,  $p < 0.001$ ). The MCID values of TNSSs and NMCCTs were 3.19 and 2.78, respectively. The cutoff value of pretreatment VAS ranged between 6.5 and 7.7 points, with an average value of 7.1. **Conclusion:** A pretreatment VAS score of 7 or higher was associated with an unfavorable treatment outcome, which suggests the potential therapeutic predictive value of VAS scoring.

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## Introduction

Allergic rhinitis is a chronic inflammatory disorder of the nasal mucosa caused by IgE-mediated hypersensitivity responses. It affects 10–30% of adults and 40% of children worldwide. Despite recent advances in pharmacotherapy, this condition can still lead to substantial impairment in quality of life, sleep, school and work performance [1, 2]. Several stepwise pharmacologic management algorithms for allergic rhinitis have been proposed; however, these guidelines have been shown to be less effective in practice than in theory [3]. A lower rate of effectiveness

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in real-world settings is, at least in part, caused by several questions and grades in the guideline scoring systems which are difficult to comply with. Several groups are attempting to propose more specific rhinitis control questionnaires [4, 5]; however, a simpler yet reliable and easy-to-apply evaluation would be more useful when administered in general practices.

The visual analogue scale (VAS) is a quantitative measure validated for use in many diseases [6]. The VAS has been incorporated into a mobile phone application (MASK-air [Mobile Airways Sentinel Network], formerly the Allergy Diary) for assessing allergic rhinitis symptoms, symptom control and work productivity [7–10]. In allergic rhinitis, several studies have found that the severity of nasal symptoms is better correlated with underlying mucosal inflammation and treatment outcome than duration [11, 12]. A VAS of overall severity of nasal symptoms, taking into consideration its impact on quality of life, would indicate disease severity and underlying mucosal inflammation. It follows that a higher VAS score should indicate more inflammation and worse treatment outcomes than a lower VAS score and thus be a suitable guide for medical treatment; however, the assumption has never been tested. To test this hypothesis, we conducted a prospective cohort study to evaluate the performance of pretreatment VAS score as a predictor of treatment outcome. Nasal mucociliary clearance time (NMCCT) was used to evaluate overall disease severity related to levels of underlying mucosal inflammation [13–15]. We first evaluated the correlation between pretreatment VAS score and the severity of disease through the use of total nasal symptoms score (TNSS), NMCCT and global symptom controls (GSCs) after treatment. We then evaluated the predictive ability of a pretreatment VAS score in relation to minimal clinically important changes in outcome scores after treatment.

## Materials and Methods

A single-center, prospective cohort study was conducted at the Allergy and Rhinology Clinic, Songklanagarind Hospital, Songkhla, Thailand, between January 1, 2010 and June 30, 2013. The protocol was approved by the Institutional Review Board of the Faculty of Medicine, Prince of Songkla University. All patients provided written informed consent prior to their enrollment.

### Study Population

All patients were aged above 15 years, had rhinitis symptoms and a positive skin prick test response to a common aeroallergens panel (Acacia, kapok, careless weed, Bermuda grass, Johnson

grass, *Dermatophagoides farinae*, *D. pteronyssinus*, *Alternaria* species, *Aspergillus* mix, *Candida albicans*, *Penicillium* mix, *Fusarium*, *Cladosporium sphaerospermum*, American cockroach, German cockroach, cat, dog and mixed feathers), defined as a wheal of  $\geq 3$  mm larger than the diluent control.

Nasal endoscopy was performed in all patients and a patient was excluded if they had symptoms and/or nasal endoscopic findings suggestive of severe septal deviation, rhinosinusitis, nasal polypoidosis and/or neoplasm. Patients who had used an antihistamine within 2–7 days, a decongestant within 2 days and intranasal, inhaled or systemic steroids within 2 months or were current smokers were also excluded from the study.

The medical history of each subject, including age, gender, nasal symptoms, concomitant diseases, and medication use, was recorded. A history of asthma was defined by a history of recurrent episodes of wheezing, shortness of breath, chest tightness, and/or coughing and a normal chest radiograph.

### Study Design

All patients were treated with triamcinolone acetonide aqueous nasal spray (Nasacort® AQ, Aventis Pharmaceuticals, Bridgewater, NJ, USA) 220  $\mu$ g/day, administered as 2 sprays/nostril once daily in the morning for 28 days. They were informed that the use of other allergy or rhinitis medications was not allowed and were asked to record carefully each dose taken on a daily diary card. All adverse events were documented and rated as mild, moderate or severe.

### Clinical Assessment

VAS score, nasal symptoms and NMCCT were evaluated for each patient at pretreatment and 28 days after treatment as follows. Overall severity of nasal symptoms, taking into consideration their impact on quality of life, was evaluated using a VAS ranging from 0 (no symptoms) to 100 mm (maximal imaginable symptoms). The patients were instructed to mark a line at the location that they found to best represent the severity of their symptoms. The score was assessed by measuring the distance from the “no symptom” end to the patient’s mark.

Nasal blockage, rhinorrhea, itchy nose, itchy eyes, sneezing, postnasal drip, facial pain/pressure and loss of sense of smell were each scored on a 7-point graded Likert scale [16] as follows: 0 (none), no symptoms; 1–2 (mild), steady but easily tolerable symptoms; 3–4 (moderate), symptoms sufficient to cause interference with daily activities; and 5–6 (severe), symptoms incapacitating daily activities. The sum of the individual symptom scores was defined as the TNSS.

The NMCCT was assessed according to Andersen et al. [17] and modified by Rutland and Cole [18]. Under nasal endoscopy, a 1- to 2-mm charcoal and saccharin powder mixture patch was placed 1 cm behind the anterior end of the inferior turbinate. During the measurement period, the patient was asked not to sniff, sneeze, eat or drink. The patient was asked to swallow every 30 s and to report the first sensation of a sweet taste. The pharyngeal wall was inspected at 15-s intervals until a charcoal appearance was observed to establish the NMCCT. The test was repeated in the other nasal passage. The average of the two times was taken as the NMCCT for the subject.

At 28 days after treatment, the GSC score was rated on a 100-percent VAS: 0% = worst possible control and 100% = best possible control.

**Table 1.** Changes in VAS score, nasal symptoms score, and NMCCTs after treatment (mean  $\pm$  SD)

| Outcome variable            | Pretreatment      | Posttreatment     | <i>p</i> value |
|-----------------------------|-------------------|-------------------|----------------|
| VAS score                   | 59.60 $\pm$ 19.35 | 25.77 $\pm$ 22.13 | <0.001         |
| <i>Nasal symptom score</i>  |                   |                   |                |
| Blocked nose                | 3.74 $\pm$ 1.17   | 1.31 $\pm$ 0.99   | <0.001         |
| Rhinorrhea                  | 3.48 $\pm$ 1.20   | 1.04 $\pm$ 0.98   | <0.001         |
| Sneezing                    | 3.39 $\pm$ 1.28   | 1.04 $\pm$ 0.96   | <0.001         |
| Nasal itching               | 2.99 $\pm$ 1.47   | 0.95 $\pm$ 1.08   | <0.001         |
| Eye itching                 | 2.34 $\pm$ 1.62   | 1.46 $\pm$ 1.73   | <0.001         |
| Postnasal drip              | 2.49 $\pm$ 1.42   | 1.56 $\pm$ 1.73   | <0.001         |
| Hyposmia                    | 1.07 $\pm$ 1.49   | 0.65 $\pm$ 1.19   | 0.029          |
| Facial pressure and/or pain | 1.37 $\pm$ 1.57   | 0.92 $\pm$ 1.62   | 0.049          |
| Total nasal symptoms score  | 20.85 $\pm$ 6.38  | 8.93 $\pm$ 7.39   | <0.001         |
| NMCCT, min                  | 18.11 $\pm$ 6.22  | 10.94 $\pm$ 3.59  | <0.001         |

#### Statistical Analysis

To have a two-tailed significance level of  $\alpha = 0.05$  and 80% power to detect correlations with a medium effect size ( $r = 0.3$ ) between pretreatment VAS score and GSC after treatment, and allowing for a 20% dropout rate, the study required at least 101 patients. The VAS scores, TNSSs and NMCCTs between pre- and post-treatment were analyzed by the unpaired *t* test and Wilcoxon signed-rank test for parametric and nonparametric data, respectively. In correlation analyses between pretreatment VAS scores and pretreatment TNSSs and NMCCT, and GSC after treatment, the Pearson and Spearman rank correlations were used for parametric and nonparametric data, respectively.

The minimal clinically important difference (MCID) is the smallest change in a score that has a clinically meaningful difference after treatment for the patient and is used to separate patients with and without improvement. A change in VAS score greater than 23 mm after treatment has been suggested in the literature as indicating a significant change [19, 20] and this cutoff point was applied in this study. One half of the standard deviation (SD), equal to a medium effect size, of pretreatment scores was used to estimate the MCIDs of TNSSs and NMCCTs [21]. Receiver operating characteristic (ROC) curves were created to evaluate the predictive ability of the pretreatment VAS scores in relation to the MCIDs in the VAS, TNSSs and NMCCTs after treatment. The maximum value of Youden's index (*J*), defined as  $J = \text{Sensitivity} + \text{Specificity} - 1$ , was used to identify the optimal cutoff pretreatment VAS score [22]. A *p* value <0.05 was considered statistically significant.

## Results

#### Patient Characteristics

One hundred and one patients, 30 males and 71 females, aged 16–59 years (mean 30.5 years) completed the study. One patient was lost to follow-up due to a traveling

problem. The duration of rhinitis symptoms was 6–35 years (mean 9.8 years). There were 8 patients with a history of asthma. Daily diary cards indicated that the mean rate of compliance with the nasal steroids was 97.1%. Ten patients experienced adverse events of mild intensity. Seven patients had local irritation and 3 patients had throat irritation. No patients reported crusting or epistaxis. No patients withdrew from the study due to adverse effects.

#### VAS, TNSSs and NMCCTs after Treatment

All VAS, TNSS and NMCCT scores showed statistically significant improvement at 28 days after treatment (Table 1).

#### Correlations between Pretreatment VAS and Pretreatment TNSSs, NMCCTs and GSC after Treatment

There were positive correlations between pretreatment VAS and pretreatment TNSS and NMCCT ( $\rho = 0.66$ ,  $p < 0.001$  and  $r = 0.44$ ,  $p < 0.001$ ; Fig. 1a, b, respectively). The GSC tended to worsen in relation to higher pretreatment VAS scores ( $r = -0.53$ ,  $p < 0.001$ ) (Fig. 1c).

#### MCID and Pretreatment VAS Cutoff Value to Discriminate between Responders and Nonresponders

The MCID values of the TNSS and NMCCT were 3.19 and 2.78, respectively. Using the sensitivity-specificity approach, the cutoff values of pretreatment VAS scores to discriminate between patients who responded and those who did not respond to treatment in relation to the MCIDs of VAS, TNSS and NMCCT are summarized in Table 2. The pretreatment VAS cutoff values ranged between 6.5 and 7.7 points, with an average value of 7.1. The areas under the ROC curves ranged between 0.82 and 0.90 (Fig. 2).

## Discussion

The VAS score is a simple psychometric measuring instrument designed to evaluate disease-related symptom severity in clinical practice [6]. Because there is a lack of a strong correlation between symptom severity and the degree of mucosal inflammation, in this study, both subjective and objective assessments were used to evaluate disease severity. The outcome measurements included subjective assessment through a VAS score and nasal symptoms, and objective assessment through NMCCTs. The pretreatment VAS scores showed a positive correla-

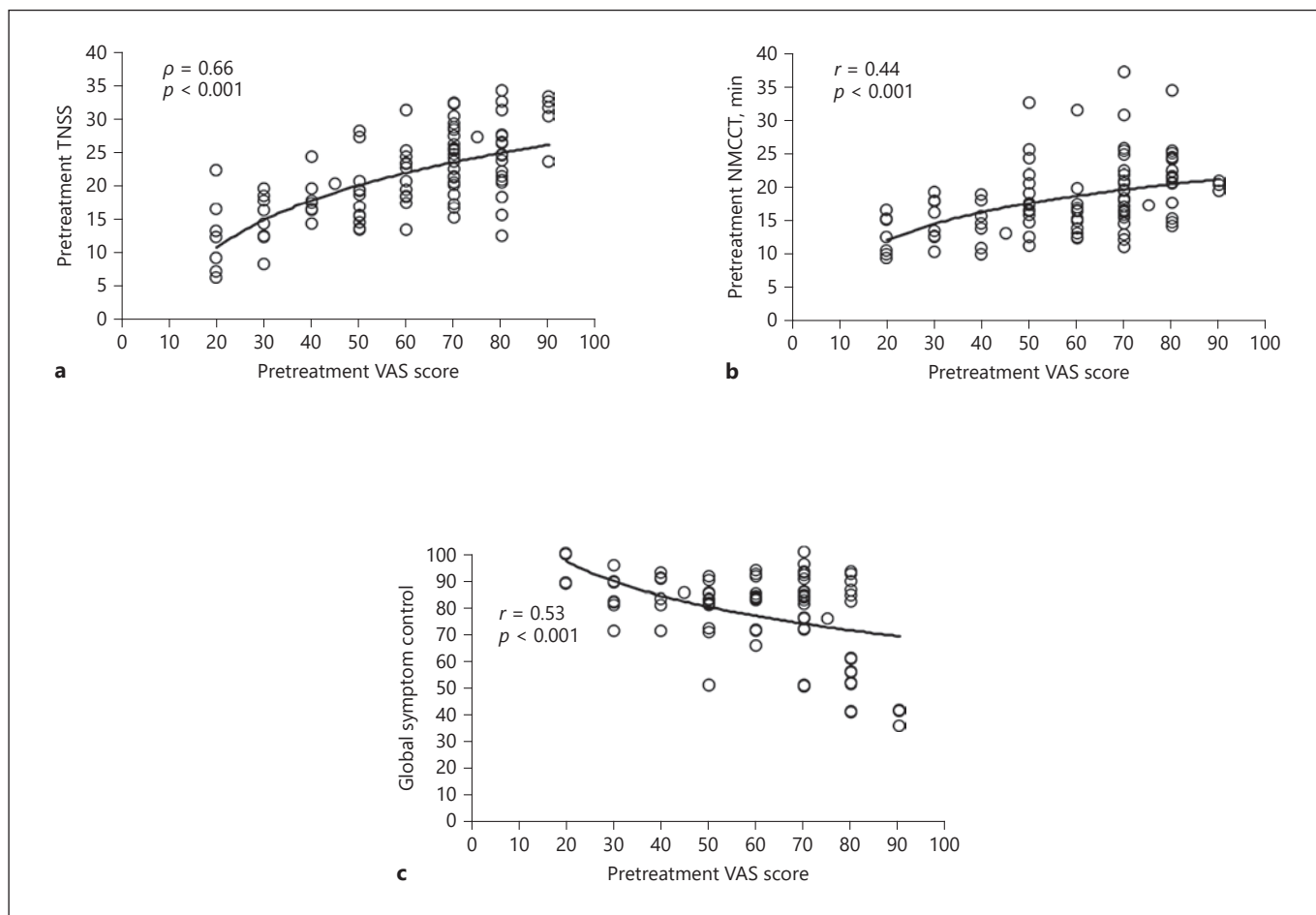


**Fig. 1.** Correlation analyses between pretreatment VAS score and pretreatment TNSS (a), pretreatment NMCCT (b) and global symptom control (c). Correlations were analyzed using Spearman ( $\rho$ ) and Pearson ( $r$ ) correlation coefficients, with 2-tailed tests of significance.

**Table 2.** The optimal cutoff values of pretreatment VAS to differentiate between responders and nonresponders using MCIDs of VAS, TNSS and MNCCT

| Outcomes | Pretreatment VAS cutoff score | Sensitivity, % | Specificity, % | Youden index | AUC (95% CI)     |
|----------|-------------------------------|----------------|----------------|--------------|------------------|
| VAS      | 6.5                           | 87.8           | 62.3           | 0.50         | 0.82 (0.73–0.92) |
| TNSS     | 7.2                           | 83.3           | 89.2           | 0.73         | 0.90 (0.82–0.98) |
| NMCCT    | 7.7                           | 73.9           | 92.3           | 0.66         | 0.89 (0.82–0.97) |

tion with TNSSs and NMCCTs. Our findings suggest that a VAS score could with reasonable reliability represent overall severity of symptoms and disease mucosa. Nasal inflammation is likely to be more severe in patients with higher VAS scores. The VAS has been found to correlate with rhinitis control, allergic multimorbidity, work im-

pairment and RQLQ (Rhinoconjunctivitis Quality of Life Questionnaire) score [23–26].

Several studies have found that VAS scores correlated well with the ARIA (allergic rhinitis and its impact on asthma) severity classification. A VAS score of 50 or 60 (on a 100-mm scale) has been associated with moderate–severe

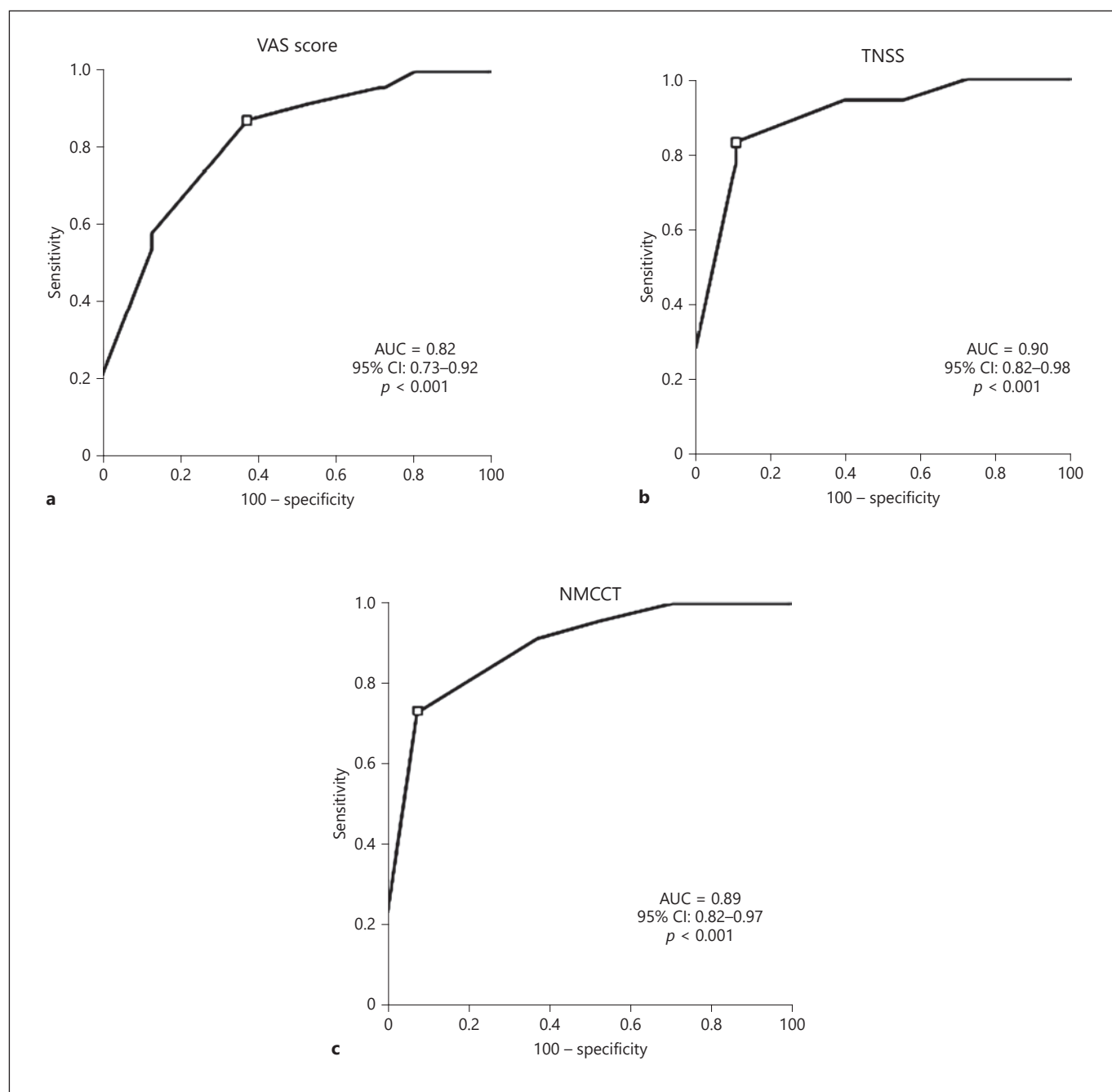


**Fig. 2.** ROC curves for the optimal cutoff point of the pretreatment VAS score to differentiate between responders and nonresponders using MCIDs of VAS score (a), TNSS (b) and NMCCT (c).

allergic rhinitis [23, 27, 28]. Allergic rhinitis patients with VAS scores that remained above 50 mm after treatment exhibited a continual pathological level in terms of quality of life and work productivity [22]. MACVIA-ARIA has proposed a simple VAS-based algorithm called the MASK clinical decision support system (CDSS) using a VAS cut-

off value to assess allergic rhinitis control and guide treatment decisions in a step-up/step-down approach. Uncontrolled allergic rhinitis is defined as a VAS score of 50 mm or greater [29–31]. However, the more important question in clinical practice is whether a pretreatment VAS score can have a reliable predictive value for treatment outcome.

To study this, we analyzed pretreatment VAS scores to determine the correlations with the patients' ratings of their GSC after treatment. The analysis found that pretreatment VAS scores were inversely correlated with GSC after treatment. It is likely that allergic rhinitis with higher VAS scores would have more inflammation, which would cause a lower therapeutic response. To identify the optimal cutoff value of pretreatment VAS score to separate patients likely to respond to treatment from those less likely to respond, ROC curves were created to evaluate the predictive ability of pretreatment VAS scores in relation to MCIDs of the outcome variables. An MCID value is the smallest change in an outcome score that indicates a clinically meaningful difference after treatment for the patient. In allergic rhinitis, other studies have suggested that a change in VAS score greater than 23 mm after treatment can be considered to be the MCID [15, 16]. In our study, the MCID values of the TNSS and NMCCT were 3.19 and 2.78, respectively. The cutoff values of pretreatment VAS score thresholds with the maximum Youden index, a measurement of a diagnostic test's ability to balance sensitivity (detecting disease) and specificity (detecting no disease), in relation to the outcome variables ranged between 6.5 and 7.7 points, with an average value of 7.1. The areas under the ROC curves ranged from 0.82 to 0.90, suggesting a good accuracy of discrimination. Overall, we found that allergic rhinitis patients with a pretreatment VAS score of 7 or more tended to have worse therapeutic responses, and patients with such high scores might need higher doses, longer treatment and/or higher-potency medications. Although further clinical studies are required for validation of this cutoff value, we believe that the severity of a patient's symptoms as indicated by a pretreatment VAS score with an optimal cutoff value could be a practical guide in the disease management approach in allergic rhinitis.

The limitation of our study was the relatively small sample size, which may limit the generalizability of the findings. However, a power analysis was performed based

on medium effect size and our sample size had enough power to show a significant negative correlation between pretreatment VAS scores and GSCs after treatment, and the results achieved clinical validity with ROC curve analysis in discriminating treatment responders from nonresponders.

In conclusion, our main findings were: (1) pretreatment VAS score was associated with the severity of the disease, including TNSS and NMCCT, (2) pretreatment VAS score had an inverse correlation with GSC, and (3) a pretreatment VAS score of 7 or higher was associated with poor treatment outcome.

### Statement of Ethics

The protocol was approved by the Institutional Review Board of the Faculty of Medicine, Prince of Songkla University (REC 60-045-13-1). Written informed consent was obtained from all patients.

### Disclosure Statement

The authors have no conflicts of interest to declare.

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### Author Contributions

Virat Kirtsreesakul contributed to the conception of the project, design, data analysis and interpretation, and to the drafting of the manuscript. Jitanong Leelapong contributed to the study design and data interpretation. All authors contributed to data acquisition, critical revision, final approval of the paper and agreed to be accountable for all aspects of the work.

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