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Patient-rated angioedema severity using a novel photo-aid for predicting non-mast cell mediator-induced angioedema diagnosis

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ABSTRACT

Background: Patients with non-mast cell mediator-induced angioedema (NM-AE) usually experience a diagnostic delay. Therefore, a clinical tool for predicting NM-AE diagnosis is essential.

Objective: To identify clinical predictors related to a confirmed diagnosis of NM-AE.

Methods: Participants with a history of recurrent AE with unknown causes were enrolled. They were classified into mast cell mediator-induced AE (M-AE) and NM-AE according to the response to anti-mast cell mediator therapy. All participants were asked to rate their worst AE ever experienced (% Photomax) from 0 to 100% using a novel photo aid. Clinical characteristics were recorded and analyzed by univariable and multivariable analysis.

Results: Thirty-five participants were included, 25 with NM-AE and 10 with M-AE. AE located at extremities, face, and genitalia and positive family history were significantly associated with NM-AE. The AE severity in the NM-AE group was significantly higher than in the M-AE group, with the mean % Photomax of 82.4 $\pm$ 20.3 vs 47.5 $\pm$ 25.6 ($p < 0.001$), respectively. Univariable analysis showed that the % Photomax (every 10% increase), feet AE and hands AE were predictive of being NM-AE with the area under the receiver operating characteristic curve (AuROC) of 0.87 (95% CI 0.75, 0.99), 0.85 (95% CI 0.72, 0.98), and 0.84 (0.69, 0.99), respectively. Multivariable analysis showed that the combination of hands AE and % Photomax enhanced diagnostic accuracy (AuROC 0.94, 95% CI 0.86, 1.0) and constituted the prototype formula for calculating the diagnostic probability.

Conclusion: Patient-rated angioedema severity using a novel photo aid combined with hands AE had a high probability of diagnosing NM-AE.

Keywords: Angioedema, Diagnosis, Hereditary angioedema, Photo aid, Predictors

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INTRODUCTION

Angioedema (AE) is a swelling of the subcutaneous layer of the skin and mucosa of internal organs, such as gastrointestinal (GI) and respiratory mucosa.[1] According to the international WAO/EAACI guideline for the management of hereditary angioedema (HAE), the 2021 revision and update, AE was classified by key mediators into 3 subtypes: mast cell mediator-induced AE (M-AE), bradykinin-induced AE (BK-AE), and idiopathic AE (I-AE).[2] M-AE was the most common subtype, with a prevalence of 45–65% of all AE.[3–5] Although BK-AE, consisting of HAE, acquired AE, and drug-induced AE, was less common, it related to a diagnostic delay and had a higher fatality.[6]

Determining the coexisting of urticaria is usually the first crucial step to distinguish AE subtypes.[1,2] Patients with non-mast cell mediator-induced AE (NM-AE) typically present with isolated AE without urticaria. However, since the prevalence of urticaria in the general population is rather common, its coexistence may be present in some patients with NM-AE. Of note, the presence of urticaria in HAE patients could be as commonly found as in non-HAE ones, with a prevalence of up to 29%.[7] Therefore, the presence of urticaria should not be solely used to exclude HAE.[2,8] Also, misinterpretation of the skin lesions by physicians and patients could complicate the diagnosis.

Bradykinin and histamine are vasoactive mediators that could modify vascular permeability. The binding of bradykinin and histamine to their receptors causes endothelial barrier disruption, allowing the fluid to leak into extracellular space.[9–11] The extravasation, however, is more prominent in the bradykinin-mediated process, leading to a more intense swelling that lasts longer.[9–11] The severe cutaneous and submucosal swelling in HAE can cause pain, disfigurement, and impaired functions.[12] The AE severity is currently used to evaluate the treatment response during acute AE episodes and monitor the disease activity during the follow-up periods.[13] To date, no studies using AE severity to predict AE subtypes exist.

We aimed to explore the possibility of using AE severity and other clinical features as potential candidates for classifying patients with isolated recurrent AE into AE subtypes.

METHODS

Study design

A single-centered, prospective cohort study was conducted from August 2020 to December 2021. The study was performed following the Declaration of Helsinki. All patients gave written informed consent. The patient in the novel photo aid gave informed consent to use her photos for conducting and publishing the study. The protocol was approved by the Institutional Review Board and Ethics Committee [approval code: 612/2562 (EC1)].

Participants

Patients with a history of recurrent AE with unknown causes were eligible to participate in the study. Obtaining clinical characteristics, potential triggers, and family history as well as thoroughly reviewing medical records were performed for initial evaluation. The exclusion criteria were participants with 1) denying informed consent or 2) an intention to leave the study before completing the diagnostic assessment.

Patient-rated maximum angioedema severity

We examined every photo taken by each patient; however, none of them, particularly those taken by a single patient, were deemed appropriate concerning the severity of the grading. Most patients only snapped images when their facial swelling was sufficiently severe to prevent them from going out in public or feeling as though their upper airways were being obstructed. From a collection of patient pictures in our cohort, 3 allergists independently chose Fig. 1A and B, which belonged to one of our patients. They concurred that Fig. 1A and B accurately depicted the degree of swelling at 0% and 100%, respectively. The proposed photo aid's main goal was to convey the sense of the most significant swelling compared to the patient's normal face to depict the severity of AE. Each participant was asked to rate their worst AE ever experienced (% Photomax) using both photos. The instruction of usage was "Please rate your worst swelling ever experienced by 0–100% compared with this photo set. Fig. 1A was no swelling at all, meaning 0% severity, and Fig. 1B

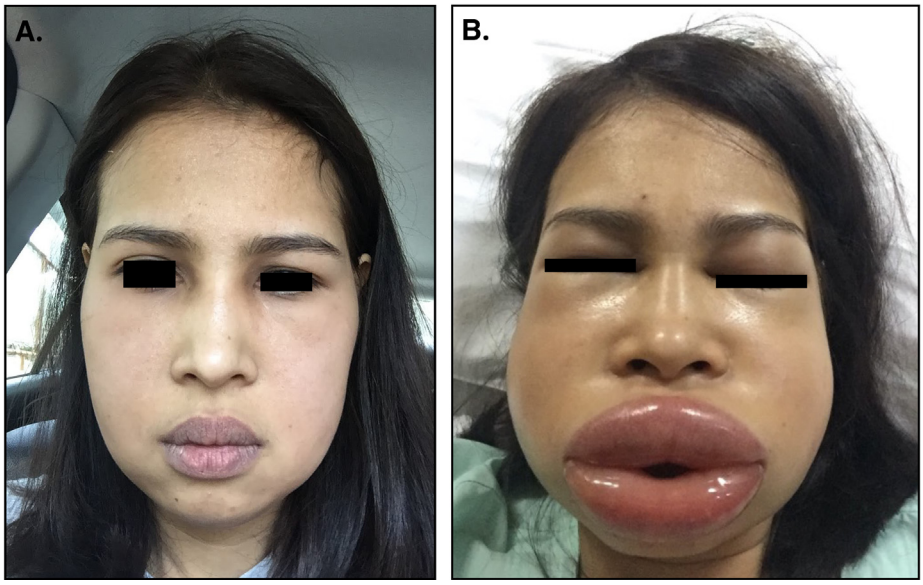

Fig. 1 The novel photo aid set. **A)** The image of a patient without angioedema (0% AE severity); **B)** The image of the same patient experiencing an acute AE attack. (100% AE severity). This photo set was used with an instruction: "Please rate your worst swelling ever experienced by 0–100% compared with this photo set. Fig. 1A was no swelling at all, meaning 0% severity, and Fig. 1B was the worst swelling experienced, meaning 100% severity"

was the worst swelling experienced, meaning 100% severity".

Diagnosis of angioedema subtypes

Patients were diagnosed with M-AE if they 1) had isolated AE after excluding common known causes, such as food, drug or insect allergy and 2) responded well to anti-allergy drugs, including antihistamines, corticosteroids, and epinephrine. AE patients not consistent with M-AE were classified into NM-AE, then subcategorized into BK-AE (HAE and acquired AE) or I-AE.

The HAE was diagnosed according to the international WAO/EAACI guideline for the management of HAE (the 2021 revision and update).[2] HAE with C1–INH deficiency was defined as type I, low C1–INH level and low C1–INH function, and type II, normal C1–INH level and low C1–INH function. Patients were also evaluated for autoimmune diseases, possible malignancies, and the use of angiotensin-converting enzyme inhibitors (ACEI) to exclude acquired AE. I-AE was a diagnosis by exclusion of HAE and acquired AE.

Laboratory investigation

All participants with suspected NM-AE were tested for a complement panel. Turbidimetric immunoassay was used to measure C4, C1–INH, and C1q concentration (Optilite®, The Binding Site, Birmingham, UK). The function of C1–INH was tested by Chromogenic assay (Technochrom® C1–INH, Technoclone, Vienna, Austria). In patients with a normal complement panel, whole genome sequencing was performed using the dried blood spot technique (Centogene®, Germany) to diagnose HAE with normal C1–INH.

Statistical analysis

All statistical analyses were conducted using Stata 17 (StataCorp, College Station, TX, USA). Continuous data are presented as mean and standard deviation (SD) or median (interquartile range, IQR) as appropriate. Categorical data are presented as frequency (%). To compare the clinical characteristics between the M-AE and the NM-AE group, we used an unpaired *t*-test or the Mann-Whitney *U* test for continuous data and the Chi-squared test or Fisher's exact test for categorical data. We explored the discriminative ability of predictors that showed statistical significance results from univariable analysis by calculating the area under the receiver operating characteristics curve (AuROC). Due to the rarity of the outcome variable and the small sample size, Firth's logistic regression was used for estimating the diagnostic

odds ratio (DOR) for each predictor to reflect the magnitude of association.[14]

For the derivation of the predictive scoring system, we performed a multivariable logistic regression using Firth's procedure with a full model approach by incorporating every potential predictor within the model. Locally-weighted scatter plot smoothing was used for checking the linearity of continuous predictors prior to statistical modeling. Then, a stepwise backward elimination of the non-significance predictor was conducted to identify the remaining independent predictors of NM-AE. AuROC was calculated from the linear predictors of both the full and reduced models. The weighted score was generated by dividing the logit coefficient of each predictor by the smallest one. The total score was equal to the sum of the weighted score from each predictor within the final model. We also created the score model for estimating the probability of being NM-AE by executing a logistic model with a total score as the independent variable.

Score performance was evaluated regarding discriminative ability using AuROC, and calibrations using Hosmer-Lemeshow goodness of fit test and calibration plots. We selected the cut-off point of the score according to the methods proposed by Liu et al.[15] Internal validation of the score model was performed with bootstrapping procedure with 1000 replications. An optimism-adjusted AuROC was estimated.

RESULTS

The study flow diagram is shown in Fig. 2. A total of 35 patients were included, 10 (28.6%) with M-AE and 25 (71.4%) with NM-AE. Of 25 patients with NM-AE, 20 were diagnosed with HAE, and 5 with I-AE. No patients consistent with HAE with normal C1–INH were found in our cohort.

Clinical characteristics between M-AE and NM-AE groups

The clinical characteristics comparing M-AE and NM-AE are shown in Table 1. Overall, the mean age of M-AE and NM-AE was 32.4 ± 12.5 and 44.7 ± 14.9 years, respectively, with the female preponderance in both groups. The NM-AE group

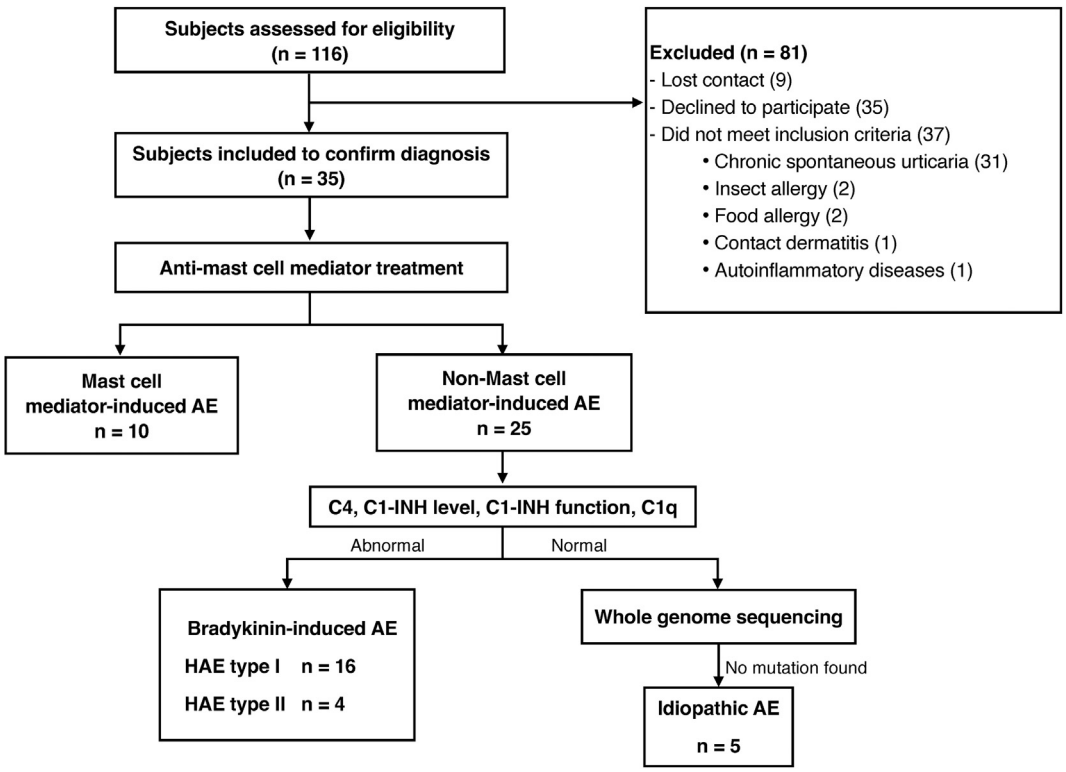

Fig. 2 Study flow diagram

Characteristics	M-AE n = 10	NM-AE n = 25	Overall n = 35	*P*-value
Female	8 (80.0)	14 (56.0)	22 (62.9)	0.227
Age, mean ± SD, y	32.4 ± 12.5	44.7 ± 14.9	41.2 ± 15.2	0.055
Age of onset, mean ± SD, y	25.9 ± 15.3	23.3 ± 13.6	24.0 ± 13.9	0.597
Diagnostic delay, median (IQR), y	2.5 (1.0–11.6)	14 (7.0–37.0)	12.0 (3.0–26.0)	0.060
Family history of recurrent AE	**3 (30.0)**	**20 (80.0)**	**23 (65.7)**	**0.010**
Cutaneous AE	9 (90.0)	25 (100.0)	34 (97.1)	0.213
Hands AE	**2 (20.0)**	**22 (88.0)**	**24 (68.6)**	**0.001**
Feet AE	**1 (10.0)**	**20 (80.0)**	**21 (60.0)**	**0.002**
Facial AE	**3 (30.0)**	**21 (84.0)**	**24 (68.6)**	**0.005**
Genitalia AE	**1 (10.0)**	**13 (52.0)**	**14 (40.0)**	**0.046**
Eyelids AE	6 (60.0)	18 (72.0)	24 (68.6)	0.476
Lips AE	7 (70.0)	14 (56.0)	21 (60.0)	0.484
Tongue AE	1 (10.0)	8 (32.0)	9 (25.7)	0.248
% Photomax, mean ± SD	**47.5 ± 25.6**	**82.4 ± 20.3**	**72.4 ± 26.8**	**<0.001**
Gastrointestinal symptoms	8 (80.0)	17 (68.0)	25 (71.4)	0.547
Respiratory symptoms	6 (60.0)	13 (52.0)	19 (54.3)	0.690

Table 1. Demographics and clinical characteristics (n = 35) *AE, angioedema; IQR, interquartile range; M-AE, mast cell mediator-induced AE; NM-AE, non-mast cell mediator-induced AE; % Photomax, the percentage of patient-rated maximum AE severity ever experienced ranging from 0 to 100% using a novel photo aid; SD, standard deviation; y, year (s). All data are presented as n (%) unless stated otherwise.*

tended to have a much longer diagnostic delay than the M-AE group, 14 (7.0–37.0) vs 2.5 (1.0–11.6) years. A family history of recurrent AE, AE at the hands, feet, face, and genitalia were significantly more predominant in the NM-AE than in the M-AE group. The severity of AE demonstrated by % Photomax was significantly higher in NM-AE than in M-AE groups, 82.4 ± 20.3% vs 47.5 ± 25.6%. The highest % Photomax was 100% in NM-AE (n = 11/25) and 80% in M-AE (n = 1/10). The median (IQR) duration from the worst AE ever experienced to the rating day was 5 (1, 6) and 12 (9, 48) months for M-AE and NM-AE, respectively. Triggers of AE, including trauma, stress, sleep deprivation, dental procedures, hormonal changes, and food, were found in 74.3% of overall patients. However, the number of those triggers was not significantly different between the two groups.

Clinical characteristics of patients with NM-AE

The clinical characteristics of NM-AE patients, 20 with HAE and 5 with I-AE, are shown in Table 2. Sixteen HAE patients were diagnosed with HAE type I and 4 with HAE type II. The mean age of onset and the mean age at diagnosis of HAE patients was 18.4 ± 9.3 and 44.3 ± 16.0 years, respectively. The median diagnostic delay was 20.5 (IQR 13–39) years. Ninety percent of patients had a family history of recurrent AE. The most common organ involvement was cutaneous AE (100%), followed by GI symptoms (80%) and airway symptoms (60%). Of 20 patients, 15 rated % Photomax with at least 80% and 10 out of 15 with 100%. The overall mean % Photomax was 85 ± 9.6%.

Another 5 patients with I-AE had a mean age of onset of 42.8 ± 9.9 years. The mean % Photomax was 72.0 ± 21.7%. They all had normal comp-

Characteristics	Hereditary angioedema[a] n = 20	Idiopathic angioedema n = 5
Female	11 (55.0)	3 (60.0)
Age, mean ± SD, y	44.3 ± 16.0	46.4 ± 9.9
Age of onset, mean ± SD, y	18.4 ± 9.3	42.8 ± 9.9
Diagnostic delay, median (IQR), y	20.5 (13–39)	4 (3–5)
Family history of recurrent AE	18 (90.0)	2 (40.0)
Cutaneous AE	20 (100.0)	5 (100.0)
Hands AE	20 (100.0)	2 (40.0)
Feet AE	18 (90.0)	2 (40.0)
Facial AE	17 (85.0)	4 (80.0)
Genitalia AE	13 (65.0)	0 (0)
Eyelids AE	13 (65.0)	5 (100.0)
Lips AE	11 (55.0)	3 (60.0)
Tongue	6 (30.0)	2 (40.0)
% Photomax, mean ± SD	85.0 ± 9.6	72.0 ± 21.7
Gastrointestinal symptoms	16 (80.0)	1 (20.0)
Respiratory symptoms	12 (60.0)	1 (20.0)

Table 2. Demographics and clinical characteristics of non-mast cell mediator-induced angioedema (N = 25) *AE, angioedema; IQR, interquartile range; % Photomax, the percentage of patient-rated maximum AE severity ever experienced ranging from 0 to 100% using a novel photo aid; SD, standard deviation; y, year (s).* [a]*Type I, n = 16 and type II, n = 4.*

lement panels and no genetic mutation identified from whole genome sequencing.

Predictive ability of candidate predictors

The DOR for predicting NM-AE with statistical significance from the univariable analysis is shown in Table 3. The % Photomax showed the highest discriminative ability based on AuROC (0.87, 95% CI 0.75, 0.99), followed by feet AE (0.85, 95% CI 0.72, 0.98) and hands AE (0.84, 95% CI 0.69, 0.99). The rest of the predictors also showed good discriminative ability.

Derivation of prediction score

No statistically significant predictors of NM-AE existed in the full multivariable logistic model. After backward elimination, two statistically significant predictors remained within the final

Candidate predictors	DOR (95% CI)	*P*-value	AuROC (95% CI)
Family history of recurrent AE	7.99 (1.65, 38.77)	0.010	0.75 (0.58, 0.92)
Cutaneous AE sites involved			
Hands	21.86 (3.60, 132.85)	0.001	0.84 (0.69, 0.99)
Feet	23.61 (3.32, 168.00)	0.002	0.85 (0.72, 0.98)
Face	10.24 (2.02, 52.02)	0.005	0.77 (0.60, 0.94)
Genitalia	6.84 (1.04, 45.10)	0.046	0.71 (0.57, 0.85)
% Photomax (every 10% increase)	1.72 (1.18, 2.50)	0.005	0.87 (0.75, 0.99)

Table 3. Univariable analysis *AE, angioedema; AuROC, area under the receiver operating characteristic curve; CI, confidence interval; DOR, diagnostic odds ratio; % Photomax, the percentage of patient-rated maximum AE severity ever experienced ranging from 0 to 100% using a novel photo aid.*

Candidate predictors	Full model		Reduced model		Beta	Score
	DOR (95%CI)	*P*-value	DOR (95% CI)	*P*-value		
Family history of recurrent AE	2.56 (0.30, 22.19)	0.394	Not included			
Cutaneous AE sites involved						
Hands	2.58 (0.10, 68.34)	0.571	12.98 (1.79, 94.04)	0.011	2.563	5.5
Feet	2.66 (0.08, 90.13)	0.586	Not included			
Face	1.98 (0.18, 22.07)	0.579	Not included			
Genitalia	1.27 (0.12.13.43)	0.845	Not included			
% Photomax (every 10% increase)	1.25 (0.76, 2.07)	0.376	1.60 (1.03, 2.49)	0.035	0.472	0.5*photomax/10
AuROC (95%CI)	0.93 (0.85, 1.00)		0.94 (0.86, 1.00)			0.93 (0.85, 1.00)

Table 4. Multivariable analysis *AE, angioedema; AuROC, area under the receiver operating characteristic curve; CI, confidence interval; DOR, diagnostic odds ratio; % Photomax, the percentage of patient-rated maximum AE severity ever experienced ranging from 0 to 100% using a novel photo aid. Example of the score calculation: Patient with hands swelling rated % Photomax of 40%; The final score = 5.5 + [(0.5x40)/10] = 7.5.*

model, hands AE (DOR 12.98; 95% CI 1.79, 94.04; p = 0.011) and each 10% increment of % Photomax (DOR 1.60; 95% CI 1.03, 2.49; p = 0.035) (Table 4). The weighted score for each feature was generated from the logit coefficients. The formula to calculate the total score is as follows:

$$\textit{Total score} = [5.5(\textit{presence of hands AE})] + \left[0.5\left(\frac{\%\textit{Photomax}}{10}\right)\right]$$

The total score ranges from 0 to 10.5. Patients with NM-AE had significantly higher scores than patients with M-AE (8.96 ± 2.28 vs 3.48 ± 2.59, p < 0.001). The higher total score was associated with a high probability of diagnosing NM-AE, as shown in Fig. 3A. The formula for estimating the probability of being NM-AE is as follows:

$$\textit{Probability of NM} - \textit{AE} = \frac{e^{-2.631527+0.5468965(\textit{Total score})}}{1+e^{-2.631527+0.5468965(\textit{Total score})}}$$

The total score showed an outstanding discriminative ability (AuROC 0.93, 95% CI 0.85, 1.00) and was well calibrated, as shown in Fig. 3B (p = 0.389 for goodness-of-fit). An optimism-adjusted AuROC was also 0.93 (95% CI 0.87, 1.00). The best cut-off score was identified at ≥7.0, given a sensitivity of 88% (95% CI 68.8, 97.5) and specificity of 90% (95% CI 55.5, 99.7).

DISCUSSION

Our cohort enrolled 35 patients with recurrent angioedema of unknown cause and classified them into 2 groups, M-AE and NM-AE, using their responses to anti-mast cell mediators medication. We compared clinical features and patient-rated angioedema severity using a novel photo aid (% Photomax) between the 2 groups. A positive family history, AE at hands, feet, face, and genitalia were more common in the NM-AE than in the M-AE groups. AE severity using % Photomax in the NM-AE group was higher than in the M-AE group. The % Photomax combined with hands AE demonstrated good diagnostic accuracy and established the formula for the probability of being NM-AE.

Our study found that the mean % Photomax was highest in the HAE group, followed by

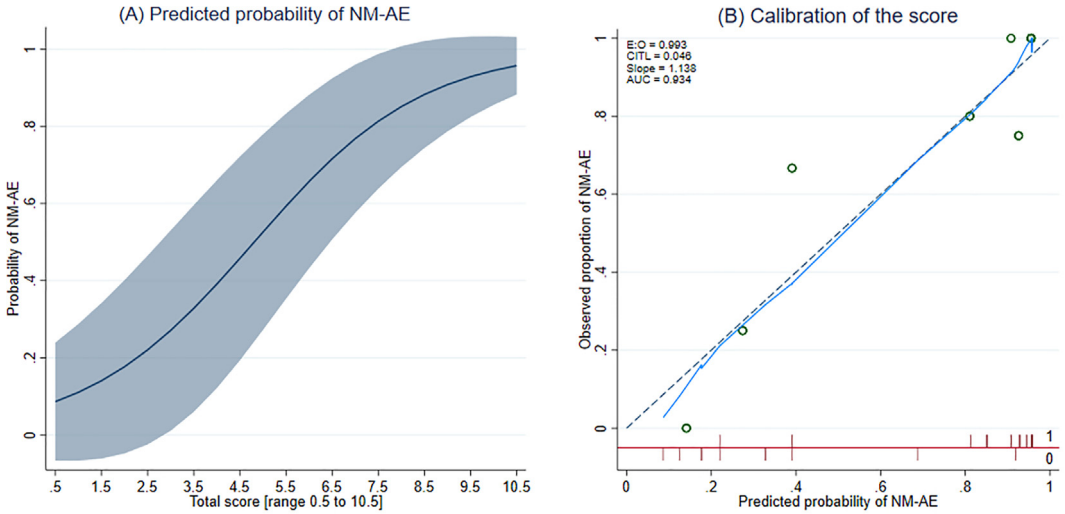

Fig. 3 A, The predicted probability of non-mast cell mediator-induced angioedema (NM-AE) across the range of the derived scoring system. **B**, Score calibration plot visualizing the agreement between predicted probability and the observed proportion of NM-AE. Dash diagonal line represents ideal calibration with a perfect agreement, whereas the solid blue line depicts the observed calibration of the score using locally-weighted scatterplot smoothing

idiopathic AE and M-AE groups. The higher the % Photomax, the more likely for being NM-AE. In addition to the AE severity, we found that the location of AE essentially mattered. Laryngeal AE is predominantly seen in BK-AE, while it has rarely been reported in M-AE.[11] Unlike M-AE, BK-AE commonly manifests AE on the face, genitalia, and extremities.[11,16] Our study found that AE in these locations was significantly associated with NM-AE, with hands AE even more dominant after performing multivariable analysis. Our findings corresponded to the Ohsawa et al[5] study, which reported that AE at extremities was significantly more frequent in NM-AE than in M-AE (80.4% vs 9.7%, $p < 0.01$). Other HAE cohorts from the United States,[17] Denmark,[18] Japan,[19] and Brazil[20] also demonstrated that extremities were the most commonly affected AE location.

Cumulative evidence of why AE mediated by bradykinin and histamine occurs in different locations has been reported. Specific biomarkers, serum endothelial selectin, and tyrosine kinase with immunoglobulin and epidermal growth factor homology domains 2 (Tie-2) were significantly associated with HAE compared with other BK-AE and M-AE.[21] The increased binding of bradykinin and bradykinin-2 receptors and the relatively increased bradykinin-1 receptor expression might also cause AE to be more common in some locations.[22,23] Taken together, the difference among mediators in their vasoactive potency, sensitivity, and distribution of their receptors, and the characteristics of endothelial tight junctions in different organs may account for AE occurring in different body sites.[24]

Using the Photomax of 80% plus hands AE for substitution in our proposed formula will yield a score of 9.5 and have a probability of diagnosis up to 90%. Given the mean % Photomax in the NM-AE group of 82.4 $\pm$ 20.3, applying our proposed formula to those patients yields a high diagnostic probability. This high-sensitivity tool would give physicians a high suspicion index, leading to early screening for the C4 level. The lower threshold to seek a definite diagnosis should mitigate the diagnostic delay. Betschel et al.[7] developed a rapid triage tool for the emergency department using the presence of recurrent AE without urticaria, past recurrent abdominal pain/swelling, and lack of response to anti-allergy treatment. This prototype tool, with a sensitivity of 98%, is beneficial for initiating prompt treatment. However, it contained some candidates being easily misinterpreted, such as the absence or presence of urticaria. To our knowledge, no clinical predictors or prediction models have ever been reported.

Our study has some strengths and limitations. The main strength is the proof-of-concept evidence for % Photomax using a novel photo

aid as a predictor for NM-AE diagnosis. The % Photomax was also used with the location of AE to develop a prototype formula for calculating the probability of being NM-AE. The proposed novel photo aid is user-friendly for patients and physicians without additional expenses. However, there were some limitations. First, the sample size was small; hence, further studies in all types of AE with a larger sample size are needed to confirm the diagnostic accuracy of the novel photo aid. Second, patient-rated angioedema severity using the proposed novel photo aid is subject to recall bias, especially if the worst swelling occurred long ago. The participants who experienced the same AE location as seen in the novel photo aid tended to rate their % Photomax higher than others. More images involving AE in various locations, different age groups, and genders should be further studied to assess the degree of swelling precisely.

In conclusion, this study first demonstrates candidate predictors for NM-AE diagnosis. The combination of hands AE and the AE severity evaluated using a novel photo aid had a high diagnostic yield. Both candidate predictors constitute the prototype formula for scoring the probability of NM-AE diagnosis with high sensitivity and specificity.

Abbreviation

AE, Angioedema; AuROC, Area under the receiver operating characteristic curve; BK-AE, Bradykinin-induced angioedema; DOR, Diagnostic odds ratios; C1–INH, C1 inhibitor; CI, Confidence interval; GI, Gastrointestinal; I-AE, Idiopathic angioedema; HAE, Hereditary angioedema; M-AE, Mast cell mediator-induced angioedema; NM-AE, Non-mast cell mediator-induced angioedema; SD, Standard deviation; % Photomax, The percentage of patient-rated maximum AE severity ever experienced.

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Availability of data and materials

The data used in this study are available from the corresponding author, on special request.

Author contributions

C.W. and T.T. conceived, designed, and conducted the research. C.W. and T.T. wrote the manuscript and had full access to all of the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis; P.P., an essentially intellectual contributor, involved in research design, data analysis, data interpretation, result summary, comprehensive comments, and writing the manuscript; T.D. involved in research design, laboratory investigation and data collection; W.S. and M.S. involved in patient recruitment, data collection and interpretation; All authors read and approved the final manuscript.

Ethics approval

The study protocol was approved by the Institutional Review Board and Ethics Committee of Siriraj Hospital [approval code: 612/2562 (EC1)] and all enrolled patients signed an informed consent for participating in the study.

Authors' consent for publication

All the Authors approved the final version of the manuscript and consent to the publication.

Declaration of competing interest

The authors declare the following financial interests/relationships which may be considered as a potential conflict of interest:

P. Phinyo and T. Dharakul declare no conflict of interest;

C. Wongsa has received honoraria for scientific lectures from A. Menarini, Astra-Zeneca, GSK, Novartis, Sanofi, Takeda, and Abbott, and research supports from Abbott and Sanofi.

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REFERENCES

1. Zuberbier T, Abdul Latiff AH, Abuzakouk M, et al. The international EAACI/GA(2)LEN/EuroGuiDerm/APAAACI guideline for the definition, classification, diagnosis, and management of urticaria. *Allergy*. 2022;77(3):734–766.
2. Maurer M, Magerl M, Betschel S, et al. The international WAO/EAACI guideline for the management of hereditary angioedema-The 2021 revision and update. *Allergy*. 2022;77(7):1961–1990.
3. Kulthanan K, Jiamton S, Boochangkool K, Jongjarearnprasert K. Angioedema: clinical and etiological aspects. *Clin Dev Immunol*. 2007;2007, 26438.
4. Nettis E, Di Leo E, Racanelli V, Macchia L, Vacca A. Idiopathic nonhistaminergic angioedema: a single-center real-life experience from Italy. *Allergy*. 2019;74(7):1389–1392.
5. Ohsawa I, Honda D, Nagamachi S, et al. Clinical and laboratory characteristics that differentiate hereditary angioedema in 72 patients with angioedema. *Allergol Int*. 2014;63(4):595–602.
6. Crochet J, Lepelley M, Yahiaoui N, et al. Bradykinin mechanism is the main responsible for death by isolated asphyxiating angioedema in France. *Clin Exp Allergy*. 2019;49(2):252–254.
7. Betschel S, Avilla E, Kanani A, et al. Development of the hereditary angioedema rapid triage tool. *J Allergy Clin Immunol Pract*. 2020;8(1):310–317.
8. Rasmussen ER, de Freitas PV, Bygum A. Urticaria and prodromal symptoms including erythema marginatum in Danish patients with hereditary angioedema. *Acta Derm Venereol*. 2016;96(3):373–376.
9. Bernstein JA, Cremonesi P, Hoffmann TK, Hollingsworth J. Angioedema in the emergency department: a practical guide to differential diagnosis and management. *Int J Emerg Med*. 2017;10(1):15.
10. Can PK, Degi Rmentepe EN, Etikan P, et al. Assessment of disease activity and quality of life in patients with recurrent bradykinin-mediated versus mast cell-mediated angioedema. *World Allergy Organ J*. 2021;14(7), 100554.
11. Maurer M, Magerl M. Differences and similarities in the mechanisms and clinical expression of bradykinin-mediated vs. Mast cell-mediated angioedema. *Clin Rev Allergy Immunol*. 2021;61(1):40–49.
12. Busse PJ, Christiansen SC. Hereditary angioedema. *N Engl J Med*. 2020;382(12):1136–1148.
13. Bork K, Anderson JT, Caballero T, et al. Assessment and management of disease burden and quality of life in patients with hereditary angioedema: a consensus report. *Allergy Asthma Clin Immunol*. 2021;17(1):40.
14. Puhr R, Heinze G, Nold M, Lusa L, Geroldinger A. Firth's logistic regression with rare events: accurate effect estimates and predictions? *Stat Med*. 2017;36(14):2302–2317.
15. Liu X. Classification accuracy and cut point selection. *Stat Med*. 2012;31(23):2676–2686.
16. Azmy V, Brooks JP, Hsu FI. Clinical presentation of hereditary angioedema. *Allergy Asthma Proc*. 2020;41(Suppl 1):18–21.
17. Bork K, Meng G, Staubach P, Hardt J. Hereditary angioedema: new findings concerning symptoms, affected organs, and course. *Am J Med*. 2006;119(3):267–274.
18. Bygum A. Hereditary angio-oedema in Denmark: a nationwide survey. *Br J Dermatol*. 2009;161(5):1153–1158.
19. Hashimura C, Kiyohara C, Fukushi JI, et al. Clinical and genetic features of hereditary angioedema with and without C1-inhibitor (C1-INH) deficiency in Japan. *Allergy*. 2021. https://doi.org/10.1111/all.15034.
20. Veronez CL, Mendes AR, Leite CS, et al. The panorama of primary angioedema in the Brazilian population. *J Allergy Clin Immunol Pract*. 2021;9(6):2293–2304.
21. Bindke G, Gehring M, Wieczorek D, Kapp A, Buhl T, Wedi B. Identification of novel biomarkers to distinguish bradykinin-mediated angioedema from mast cell-/histamine-mediated angioedema. *Allergy*. 2022;77(3):946–955.
22. Dyga W, Obtulowicz A, Mikolajczyk T, Bogdali A, Dubiela P, Obtulowicz K. The role of bradykinin receptors in hereditary angioedema due to C1-inhibitor deficiency. *Int J Mol Sci*. 2022;23(18). https://doi.org/10.3390/ijms231810332.
23. Hofman ZL, Relan A, Zeerleder S, Drouet C, Zuraw B, Hack CE. Angioedema attacks in patients with hereditary angioedema: local manifestations of a systemic activation process. *J Allergy Clin Immunol*. 2016;138(2):359–366.
24. Debreczeni ML, Nemeth Z, Kajdacsi E, Farkas H, Cervenak L. Molecular dambusters: what is behind hyperpermeability in bradykinin-mediated angioedema? *Clin Rev Allergy Immunol*. 2021;60(3):318–347.